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EFFECT OF THE PATENT DUCTUS ARTERIOSUS ON THE PULMONARY BLOOD FLOW, BLOOD VOLUME, HEART RATE, BLOOD PRESSURE, ARTERIAL BLOOD GASES AND pH

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THE analogy between patency of the ductus arteriosus and other forms of intracardiac or peripheral arteriovenous fistula has been discussed by several authors.[1-3] The effect of this abnormal communication between the aorta and the pulmonary artery upon the systemic or pulmonary circulation has been the subject of several studies,[4-8] but these usually have been restricted to isolated aspects of disturbed circulatory function.

The purpose of this paper is to report studies on (1) the degree of arteriovenous flow through the patent ductus, (2) the blood volume before surgical closure and the effect of closure on the blood volume, (3) the heart rate and the blood pressure and pulse pressure in the presence of patency and the effect of closure upon them, especially in relation to exercise, and (4) the oxygen saturation, CO_2 combining power, CO_2 tension, and pH of the blood before and after surgical closure of the patent ductus arteriosus.

1. Arteriovenous Flow Through the Patent Ductus Arteriosus.—The shunt through the ductus was determined by estimation of the blood flow through the pulmonary artery before and after ligation, using the Fick method, as described by Burwell, Eppinger and Gross.[4] The application of this can be shown as rate of pulmonary blood flow,

$$\text{l./min.} = \frac{O_2 \text{ consumption, cc./min.}}{\text{Brachial arterial } O_2 \text{ content} - \text{Pulmonary arterial } O_2 \text{ content, cc./l.}}$$

The flow through the patent ductus is the pulmonary flow before closure minus pulmonary flow after closure. The shunt through the patent ductus therefore can be expressed either as diminution of pulmonary blood flow or directly as shunted flow in liters per minute or as per cent of cardiac output. Some inaccuracies are introduced by the use of preoperative

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values for oxygen consumption, by the presence of the anesthetic gas, and by the open thorax, since samples of pulmonary artery blood were taken directly from the pulmonary artery at the time of surgery. In addition, the preoperative sample may not be representative, since complete mixing of the arterial blood from the aorta and the venous blood in the pulmonary artery may not have taken place. These problems have been discussed in

TABLE 1

ARTERIO-VENOUS OXYGEN DIFFERENCE AND CALCULATED RATE OF BLOOD FLOW THROUGH PATENT DUCTUS ARTERIOSUS; OXYGEN ANALYSIS WITHOUT REMOVING ETHER FROM BLOOD

No.	Patient	Age yr.	Arterio-venous O_2 difference		Rate of pulmonary blood flow			Ductus flow as per cent of cardiac output. Preligation	Cardiac index after ligation
			Before ligation	After ligation	Before ligation	After ligation	Decrease or flow through ductus		
			ml./100 ml.	ml./100 ml.	l./min.	l./min.	l./min.	%	l./m.²/min.
1	C.P.	3	2.04	5.36	4.90	1.87	3.03	61.8	3.28
2	M.M.	6	1.66	3.27	6.14	3.12	3.02	49.2	5.03
3	D.S.	3	1.54	2.71	6.81	3.88	2.93	43.0	6.93
4	M.B.	4	2.17	2.97	5.80	4.24	1.56	26.9	6.33
5	J.F.	6	1.23	1.53	14.15	11.37	2.78	19.6	14.04
6	K.K.	8	1.54	2.03	10.59	8.03	2.56	24.2	9.24
7	B.S.	10	1.49	3.38	10.97	4.79	6.18	56.3	5.14
8	H.B.	11	1.50	2.40	11.93	7.46	4.47	37.5	6.49
9	V.A.	14	1.58	2.42	11.70	7.65	4.05	34.6	5.50
10	E.S.	32	1.78	3.04	10.87	6.36	4.51	41.4	4.38

TABLE 2

ARTERIO-VENOUS OXYGEN DIFFERENCE AND CALCULATED RATE OF BLOOD FLOW THROUGH PATENT DUCTUS ARTERIOSUS; OXYGEN ANALYSIS AFTER ETHER REMOVAL BY METHOD OF SHAW AND DOWNING[9]

No.	Patient	Age yr.	Arterio-venous O_2 difference		Rate of pulmonary blood flow			Ductus flow as per cent of cardiac output. Preligation	Cardiac index after ligation
			Before ligation	After ligation	Before ligation	After ligation	Decrease or flow through ductus		
			ml./100 ml.	ml./100 ml.	l./min.	l./min.	l./min.	%	l./m.²/min.
1	C.P.	3	2.22	4.95	4.51	2.02	2.49	55.2	3.55
2	M.M.	6	1.49	2.81	6.84	3.63	3.21	46.9	5.85
3	I.T.	19	3.09	3.90	9.65	7.65	2.00	20.7	4.07
4	V.L.	21	1.61	2.63	13.35	8.17	5.18	38.8	5.14

detail.[4] In two cases the effect of the anesthetic agent, ether, upon the determination was tested by analysis both before and after extraction of the contaminating gas by use of the Hempel pipette.[9] These figures indicate that small positive errors of 6.6% and 2.3%, respectively, were introduced in the determination when the presence of ether was ignored.

Table 1 shows the results without taking into consideration the anesthetic agent, and table 2 shows four cases in which the calculations were based upon removal of ether. Cases 1 and 2 in the tables show results based upon both methods.

2. Blood Volume.—The blood volume was determined by the dye method, using the blue dye, T-1824, and the technic described by Gibson and Evans[10] and by Gibson and Evelyn.[11]

Table 3 shows changes in the blood volume in 13 cases following surgical closure of the open ductus, the postoperative value being determined 2 to 3 weeks after operation. Table 4 shows similar determinations in 7 cases 2 to 10 months after surgical closure. In

TABLE 3

HEMATOCRIT, PLASMA AND WHOLE BLOOD VOLUMES BEFORE AND 2 TO 3 WEEKS AFTER LIGATION OF PATENT DUCTUS ARTERIOSUS

No.	Patient	Age yr.	Hematocrit			Plasma volume			Whole blood volume		
			Before	After	Difference	Before	After	Difference	Before	After	Difference
			%	%	%	ml.	ml.	ml.	ml.	ml.	ml.
1	D.S.	3	38.7	36.6	−2.1	656	617	− 39	1069	973	− 96
2	B.S.	10	41.1	38.7	−2.4	1448	1420	− 28	2459	2316	−143
3	J.F.	6	39.0	40.9	+1.9	1235	1128	−107	2028	1908	−120
4	E.J.	32	46.0	41.7	−4.3	2808	2749	− 59	5200	4715	−485
5	M.B.	4	35.4	38.6	+3.2	975	953	− 22	1507	1552	+ 45
6	K.K.	8	38.4	40.4	+2.0	1390	1135	−255	2256	1904	−352
7	H.B.	11	39.0	39.1	+0.1	2006	1916	− 90	3335	3146	−189
8	C.P.	3	41.2	42.5	+1.3	637	584	− 53	1083	1015	− 68
9	D.W.	4	38.9	35.7	−3.2	702	795	+ 93	1149	1236	+ 87
10	C.O.	7	41.5	39.9	−1.6	1118	1281	+163	1911	2133	+222
11	F.V.		41.6	40.7	−0.9	813	734	− 79	1392	1241	−151
12	N.F.	13	41.9	39.4	−2.5	2093	2274	+181	3603	3754	+151
13	M.C.	5	37.8	35.5	−2.3	1067	1018	− 49	1715	1579	−136
	Mean				−0.8			− 26			− 95

TABLE 4

HEMATOCRIT, PLASMA AND WHOLE BLOOD VOLUMES BEFORE AND 2 TO 10 MONTHS AFTER LIGATION OF PATENT DUCTUS ARTERIOSUS

No.	Patient	Age yr.	Hematocrit			Plasma Volume			Whole Blood Volume		
			Before	After	Difference	Before	After	Difference	Before	After	Difference
			%	%	%	ml.	ml.	ml.	ml.	ml.	ml.
1	D.S.	3	38.7	39.4	+0.7	656	541	−115	1069	965	−104
2	B.S.	10	41.1	41.7	+0.6	1448	1432	− 16	2459	2339	−120
3	J.F.	6	39.0	40.1	+1.1	1235	1015	−220	2028	1754	−264
4	E.J.	32	46.0	47.1	+1.1	2808	2449	−359	5200	4629	−571
5	V.A.	14	40.5	42.9	+2.4	2340	2215	−125	3933	3836	− 97
6	I.T.	19	48.4	49.8	+1.4	3237	3205	+ 18	6270	6480	+210
7	V.L.	24	37.0	35.6	−1.4	3021	3072	+ 51	4792	4768	− 24
	Mean				+0.8			−109			−139

four of these, the blood volume had been determined also at the early period and the values for the two periods may be compared.

Chart 1 shows the volume expressed as per cent deviation from the postoperative volume.

Chart 2 shows the results of an attempt to correlate the blood volume with (1) the size of the ductus, (2) the cardiac enlargement and (3) the pulse pressure. The size of the ductus is difficult to determine with accuracy, since it is not a simple tube but usually has a

conical shape with the wide end at the aortic insertion. Other variations also occur, and the outside diameter is not necessarily an accurate index of the lumen. The gradations of small, medium and large are arbitrary. One was obviously abnormally large and four were ob-

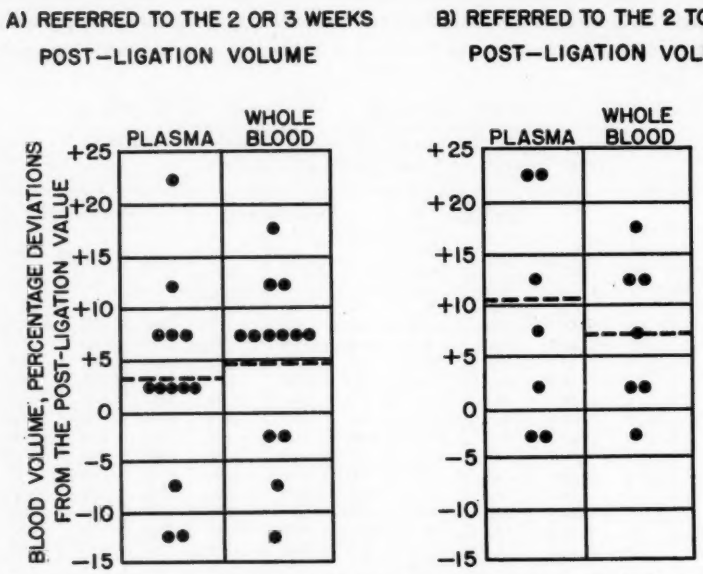

CHART 1. Distribution of percentage deviations of plasma and whole blood volumes from corresponding volumes after ligation of ductus.

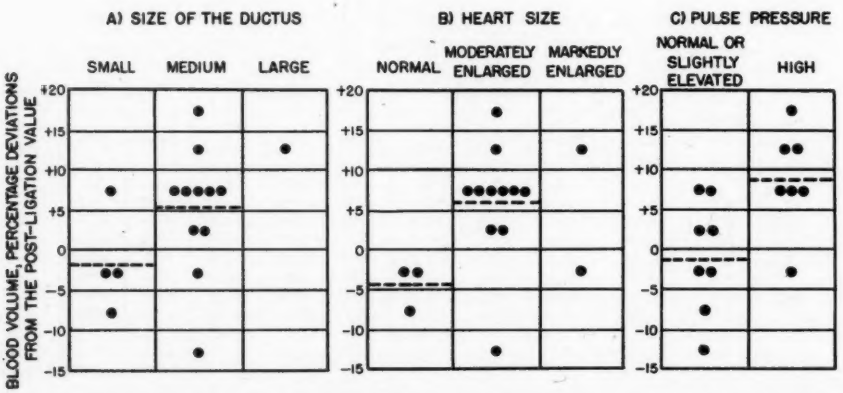

CHART 2. Distributions of percentage deviations of preoperative from postoperative blood volumes in relation to (a) size of ductus, (b) heart size and (c) pulse pressure.

viously small. The remainder were classified as of medium size. The absence of correlation between the degree of shunt through the ductus and the blood volume is shown in chart 3. Chart 4 shows the flow through the patent ductus calculated in terms of

l./m.²/min. plotted against blood volume deviation from the postligation volume. Assuming the postligation volume represents the normal volume, the deviation then expresses the increase associated with patency of the ductus. A relation is suggested, but is not statistically valid.

3. Heart Rate and Blood Pressure in the Presence of Patency.—The effect of exercise on the heart rate before and after ligation was studied. The conditions of exercise were

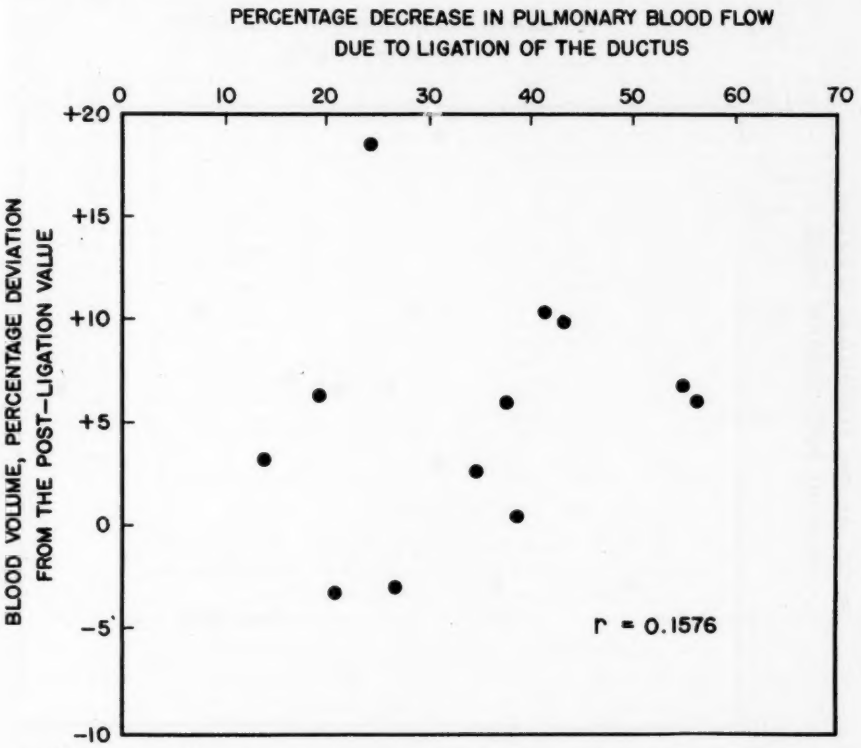

CHART 3. Showing lack of correlation between change in blood volume and decrease in pulmonary blood flow due to ligation of patent ductus arteriosus.

standard in most cases, the subject walking on an electrically driven treadmill at 3 mph, with a grade of 8.6 degrees. The heart rate was recorded by a cardiotachometer. Chart 5A shows the composite result in seven subjects walking for 10 minutes. After recovery from the walk, three of these then ran at 6 or 7 mph. The recovery from the previous exercise was not complete, as far as the heart rate was concerned, as indicated by the discrepancy in the standing heart rate. Chart 5B shows comparative rates during and following running exercise.

The effect of ligation on resting pressure, the pulse pressure and the relative values during recovery from exercise are shown in chart 6.

4. Effect of Ligation on the Arterial Blood Gases, and pH_a.—Samples of arterial blood were obtained preoperatively and two to three weeks postoperatively in 20 cases of pa-

tency of the ductus arteriosus. The oxygen and carbon dioxide contents of the blood as drawn and of samples equilibrated for 20 minutes at 37°C. in tonometers containing carbon dioxide and oxygen at approximate tensions of 40 mm. and 185 mm. of mercury, respectively, were determined by the manometric method of Van Slyke and Neill.[12] From these data and the gas contents of the tonometers, determined by Haldane analysis,[13] the oxygen saturation, carbon dioxide combining power (T40) of the blood and plasma, and

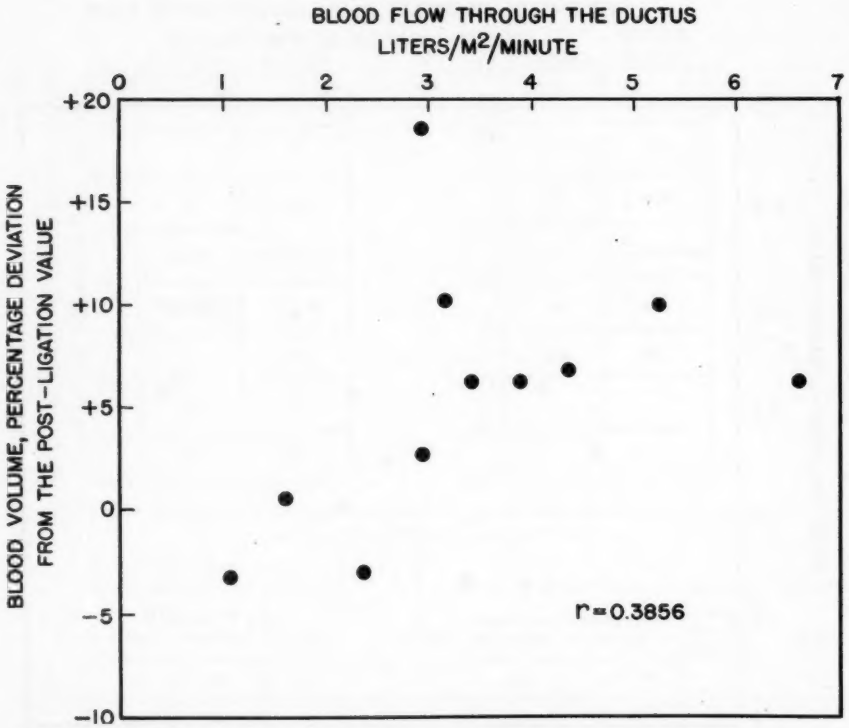

CHART 4. Blood flow through patent ductus arteriosus plotted against deviation of blood volume from postligation volume.

the pH_s were calculated by methods described by Dill, Graybiel, Hurtado and Taquini.[14] Seven cases were studied 2 to 10 months postoperatively. Four of these had been studied previously at the early period.

Tables 5 and 6 show the results of the pre- and postoperative studies.

DISCUSSION

The material presented is not a complete study of the effect of the abnormal circulation initiated by patency of the ductus upon cardiovascular dynamics. The effects upon the heart itself, especially as determined by recording of intracardiac pressure, and illustrated by occasional failure in infancy, and by changes in cardiac silhouette and ECG have not been included in this study. Some of the data, especially those related to the effect of exercise

TABLE 5

O_2 Saturation, CO_2 Combining Power, CO_2 Tension and pH_s of Arterial Blood in Patients with Patent Ductus Arteriosus, Before and 2 to 3 Weeks After Ligation of Ductus

No.	Patient	Age Yr.	O_2 Saturation			Plasma CO_2 Combining Power			CO_2 Tension			pHs		
			Before	After	Δ	Before	After	Δ	Before	After	Δ	Before	After	Δ
			Per cent			ml./100 ml.			mm.Hg					
1	L.R.	2	99.7	93.7	−6.0	50.4	50.9	+ 0.5	34.8	35.6	+ 0.8	7.383	7.384	+0.001
2	J.N.	2	95.9	93.3	−2.6	47.5	53.1	+ 5.6	32.2	22.0	−10.2	7.382	7.553	+0.171
3	D.S.	3	97.2	91.9	−5.3	50.9	51.5	+ 0.6	33.0	36.2	+ 3.2	7.402	7.388	−0.014
4	C.P.	3	96.9	93.7	−3.2	53.8	50.3	− 3.5	31.3	40.0	+ 8.7	7.448	7.344	−0.104
5	J.T.	3	95.5	93.5	−2.0	53.4	54.6	+ 1.2	33.0	33.5	+ 0.5	7.428	7.437	+0.009
6	E.S.	3	95.9	93.6	−2.3	46.8	53.1	+ 6.3	27.9	33.0	+ 5.1	7.416	7.433	+0.017
7	M.B.	4	94.2	91.5	−2.7	55.1	54.7	− 0.4	37.4	37.1	− 0.3	7.405	7.404	−0.001
8	D.W.	4	98.0	92.0	−6.0	55.9	55.4	− 0.5	32.4	35.5	+ 3.1	7.461	7.427	−0.034
9	D.P.	4	96.7	96.2	−0.5	50.4	51.8	+ 1.4	33.5	40.8	+ 7.3	7.394	7.313	−0.081
10	F.V.	4	87.5	84.9	−2.6	53.6	56.1	+ 2.5	43.9	40.8	− 3.1	7.347	7.385	+0.038
11	M.M.	6	95.9	98.7	+2.8	55.7	53.8	− 1.9	28.6	20.2	− 8.4	7.513	7.475	−0.038
12	C.O.	7	95.8	95.2	−0.6	53.2	61.8	+ 8.6	39.8	39.2	− 0.6	7.385	7.408	+0.023
13	J.J.	7	97.8	94.0	−3.8	54.7	56.1	+ 1.4	24.2	21.6	− 2.6	7.535	7.584	+0.049
14	K.K.	8	96.7	92.3	−4.4	49.3	59.3	+10.0	38.5	30.4	− 8.1	7.346	7.509	+0.163
15	S.T.	9	95.4	91.6	−3.8	57.1	60.0	+ 2.9	42.7	37.1	− 5.6	7.382	7.450	+0.068
16	B.S.	10	96.6	91.4	−5.2	55.9	56.4	+ 0.5	32.1	41.6	+ 9.5	7.462	7.387	−0.075
17	H.B.	11	92.3	93.5	+1.2	53.6	53.4	− 0.2	36.1	32.0	− 4.1	7.407	7.443	+0.036
18	N.F.	13	94.3	92.8	−1.5	57.9	63.3	+ 5.4	35.3	28.7	− 6.6	7.449	7.557	+0.108
19	E.J.	32	95.0	92.8	−2.2	58.5	59.2	+ 0.7	38.6	40.2	+ 1.6	7.425	7.417	−0.008
20	J.B.	35	89.8	94.7	+4.9	55.6	56.5	+ 0.9	36.5	40.0	+ 3.5	7.418	7.397	−0.021
	Mean				−2.29			+ 2.10			− 0.3			+0.015

TABLE 6

O_2 Saturation, CO_2 Combining Power, CO_2 Tension and pH_s of Arterial Blood in Patients with Patent Ductus Arteriosus, Before and 2 to 10 Months After Ligation of Ductus

No.	Patient	Age Yr.	O_2 Saturation			Plasma CO_2 Combining Power			CO_2 Tension			pHs		
			Before	After	Δ	Before	After	Δ	Before	After	Δ	Before	After	Δ
			Per cen			ml./100 ml.			mm.Hg					
1	D.P.	4	96.7	99.3	+2.6	50.4	46.6	−3.8	33.5	32.6	−0.9	7.394	7.364	−0.030
2	B.S.	10	96.6	92.7	−3.9	58.5	57.8	−0.7	32.1	38.2	+6.1	7.462	7.392	−0.070
3	V.A.	14	97.4	95.4	−2.0	55.9	54.1	−1.8	36.6	38.4	+1.8	7.405	7.404	−0.001
4	I.T.	19	95.4	95.9	+0.5	55.1	54.9	−0.2	41.3	40.6	−0.7	7.404	7.413	+0.009
5	V.L.	21	93.9	90.7	−3.2	55.6	54.5	−1.1	34.7	40.0	+5.3	7.432	7.384	−0.048
6	E.J.	32	95.0	96.6	+1.6	58.7	59.2	+0.5	38.6	43.7	+5.1	7.425	7.380	−0.045
7	J.B.	35	89.8	91.4	+1.6	54.9	55.7	+0.8	36.5	36.4	−0.1	7.418	7.414	−0.004
	Mean				−0.4			−0.9			+2.2			−0.027

on the heart rate and blood pressure, are limited in number of subjects. The great majority of a series of about 50 cases coming to surgery were in a young age group, and few of these were sufficiently cooperative to undertake exercise.

1. Arteriovenous Flow: In the study related to the degree of arteriovenous flow, it has been assumed that the direction of flow was entirely from aorta to pulmonary artery, even in the absence of coarctation of the aorta in any of the cases. It is quite possible that under

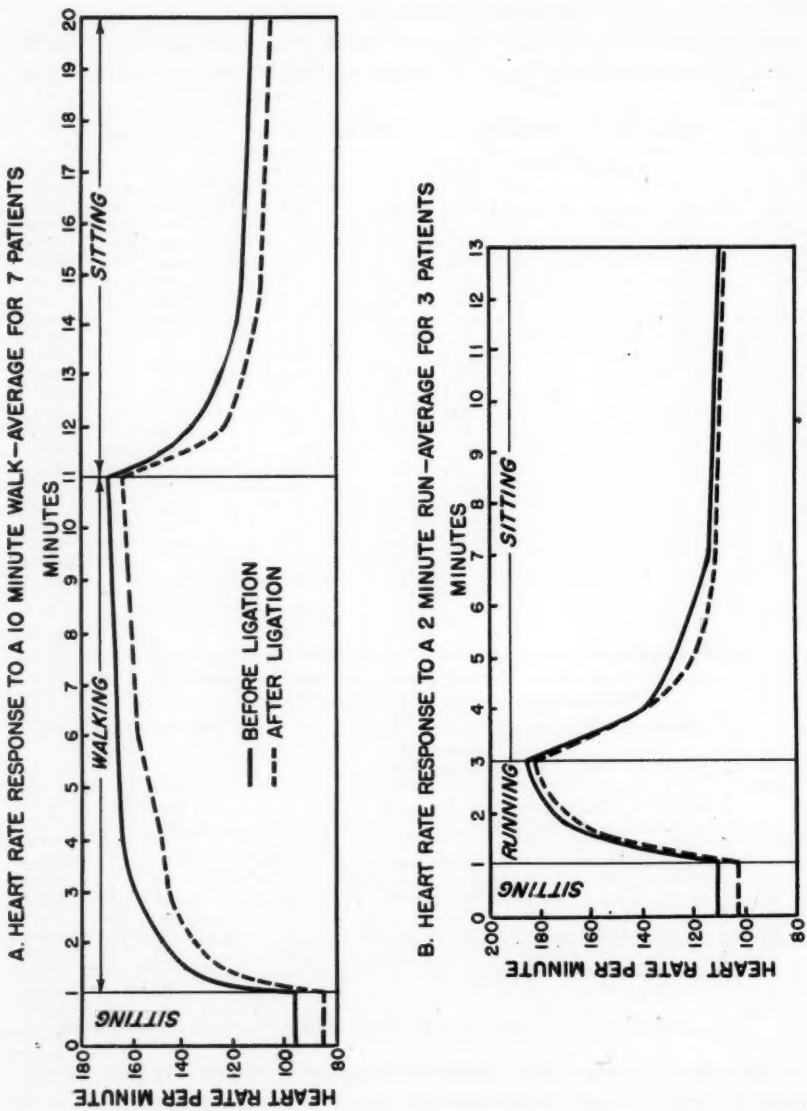

CHART 5. Heart rate response to exercise before and several months after ligation of patent ductus arteriosus.

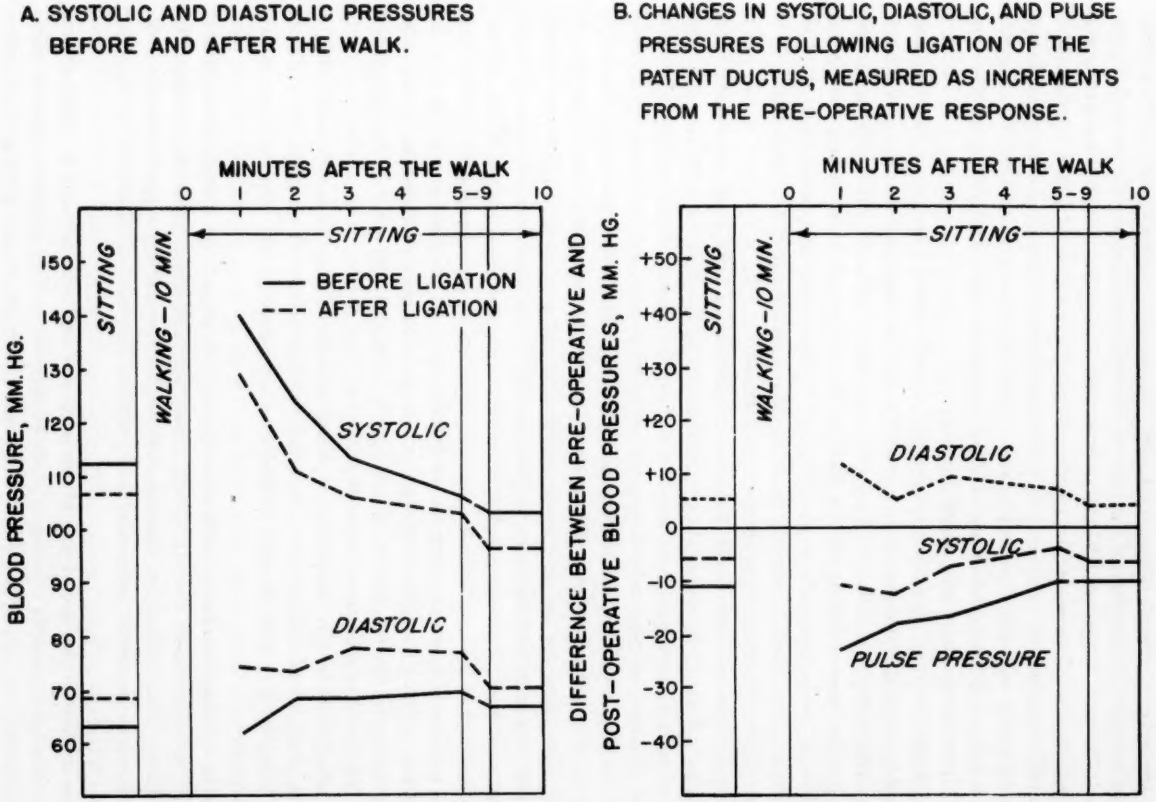
A. SYSTOLIC AND DIASTOLIC PRESSURES BEFORE AND AFTER THE WALK.
B. CHANGES IN SYSTOLIC, DIASTOLIC, AND PULSE PRESSURES FOLLOWING LIGATION OF THE PATENT DUCTUS, MEASURED AS INCREMENTS FROM THE PRE-OPERATIVE RESPONSE.
MINUTES AFTER THE WALK
0 1 2 3 4 5–9 10
SITTING
WALKING – 10 MIN.
BLOOD PRESSURE, MM. HG.
150 140 130 120 110 100 90 80 70 60
BEFORE LIGATION
AFTER LIGATION
SYSTOLIC
DIASTOLIC
DIFFERENCE BETWEEN PRE-OPERATIVE AND POST-OPERATIVE BLOOD PRESSURES, MM. HG.
+50 +40 +30 +20 +10 0 -10 -20 -30 -40
PULSE PRESSURE

CHART 6. Blood pressure before and several months after ligation of patent ductus arteriosus, in resting state and after grade walking for 10 minutes. Average for 7 patients.

circumstances of exercise or pulmonary disease the pulmonary artery pressure could be elevated sufficiently to cause flow into the aorta during some phase of the cardiac cycle. Holman[2] adduced indirect evidence that the flow could be in this direction. The present authors' material, however, and the data of Burwell, Eppinger and Gross[4] and Taylor, Pollack, Burchell, Clagett and Wood[5] indicate that in the cases studied the arteriovenous flow was usually of considerable magnitude. While there are no detailed studies available regarding changes in the peripheral flow to the extremities following closure of the ductus, there have been no changes in oscillometer readings in a few cases studied. This suggests that in spite of the large arteriovenous shunt through the open ductus the peripheral flow to the lower extremities is maintained normally.

2. Blood Volume: Burwell, Eppinger and Gross[4] studied changes in blood volume following surgical formation of an artificial ductus in dogs, and changes in the blood volume following closure in patients. Cassels and Morse[3] presented pre- and postoperative data in eight cases and compared the blood volume in preoperative patients with normal subjects of comparable surface area. Others[15,16] have reported determination of blood volume in a few cases. In general, there has been agreement that the volume tends to be elevated in the presence of the patent ductus arteriosus.

The data presented previously[3] have been augmented by 4 additional cases studied 2 to 3 weeks postoperatively and by 4 cases studied 2 to 10 months postoperatively. Examination of table 3 shows that of 13 cases, 10 had smaller plasma volumes and 9 had smaller blood volumes postoperatively. Average decreases of 26.5 cc. and 95.0 cc. for plasma and total blood volumes, respectively, are of questionable significance statistically. Tested by Fisher's "t" test, $t = 0.83$ and 1.77, or $P = 0.4$ and 0.1, respectively. This means that the range of variation and the distribution of the deviations are such that differences between the means as large as those noted might occur by chance alone over 40 times in 100 in regard to plasma and 10 times in 100 when related to total blood volume. Table 4 shows the determinations 2 to 10 months after surgery. The average decreases are greater than those noted in the earlier postoperative period, 109.4 cc. for plasma, and 138.6 cc. for total blood volume. The differences again are of questionable significance due to the range of variation and the few number of cases studied, for $t = 2.00$ and 1.54 for plasma and total blood volume differences, respectively.

In chart 1, where the changes are expressed in terms of percentage deviation from the postoperative blood volumes, the mean difference in volume of +4.6% appears more significant, for $t = 2.01$. A mean difference as large as this could arise by chance only 8 times in 100.

In the four cases studied in both an early and a late period, the average decreases were greater both for plasma and total blood volume after the longer period of circulatory readjustment. The trend of the volumes downward postoperatively suggests that the problem should be restudied, using a standard postoperative period of adjustment, perhaps one year.

The relation of the size of the ductus, heart size and pulse pressure to blood volume deviations from postoperative values is shown in chart 2. This suggests a possible correlation between the size of the ductus and blood volume deviations, although a difference of 7.2% units between a group having a small ductus and a group having a larger one is hardly significant, for $t = 1.71$. Statistical examination in this case is not satisfactory because of the inadequate numbers involved. When blood volume deviations are compared

with heart size increase in blood volume tends to be associated with moderate or marked enlargement. Proof of statistical significance is impossible because the group with no enlargement is small. The most significant correlation is that between blood volume and blood pressure. Higher pulse pressure tends to be related to increased blood volume, since $t = 3.51$ and P is less than 0.01.

Correlation could reasonably be expected between the degree of shunt through the open ductus arteriosus and elevation of the blood volume. A correlation coefficient between these two measurements of 0.1575, as shown in chart 3, does not give evidence of such relationship. The relation between blood volume deviations from the normal and ductus flow per unit of body surface appears closer, with a correlation coefficient of 0.3876 as shown in chart 4. It is conceivable that the relationship is masked because of experimental errors in either determination, especially in the measurement of the degree of shunting. More accurate methods, applied in a larger number of cases, would be required before the presence or absence of a relationship between blood volume and degree of shunt could be established.

3. Heart Rate and Blood Pressure: The effect of the patent ductus arteriosus on the heart rate is apparent in chart 5. Closure was followed by reduction of the heart rate in the patient at rest in all cases. The diminution averaged 11 beats/min. in the sitting position and 14 beats/min. in the standing position. During walking exercise the diminution of rate averaged 5 to 14 beats/min., the variation in rate depending on the minute of exercise considered. The maximum response to walking exercise was attained more slowly after the ductus was closed. During the recovery period after walking, the mean curves follow parallel courses before and after ligation, except that the postclosure curve fell a little more rapidly during the second half of the first minute. During running exercises the pre- and postoperative rates showed little difference, except that the elevation of the heart rate above pre-exercise rates was greater when the ductus was closed. There was little difference in acceleration to meet maximum demands. During recovery from running the average heart rate decreased at equal rates during the first minute after exercise, but in the second minute the postligation rate fell more rapidly. After the third minute the average recovery curves follow parallel courses, but the difference between pre- and postligation heart rates was never so great as in the pre-exercise period.

The cause of the increased heart rate in the presence of an open ductus is not clear. Leeds[17] has discussed the possible reflex mechanisms causing slowing of the heart rate following closure of experimentally produced chronic patent ductus arteriosus in dogs, and suggests the slowing of the pulse is concomitant with decrease of cardiac output. It is not clear whether the bradycardia following closure of a peripheral arteriovenous fistula[18] is caused by the same mechanism. Lewis and Drury[19] showed that this fall is vagal in origin since it is abolished by atropinization. Since the pulmonary artery and right ventricular pressure is sometimes increased,[20,21] it is possible that this increased pressure may be reflected backward into the great veins, initiating the cardio-accelerator Bainbridge reflex,[22] even at rest, but especially during stress. This may be the explanation of the slower attainment of the maximum response to exercise and the slightly more rapid recovery in the surgically treated patients.

The change in resting blood pressure following ductus closure was often, but not invariably, marked. Although in the majority of cases the diastolic pressure rose after ligation, in two patients the diastolic level was lower than before ligation. The systolic level

tended to fall following closure of the ductus. In one patient the lowering of the systolic level was marked. The average response of the resting blood pressure to ligation of the ductus was found to be a decrease in pulse pressure of 11.1 mm. of mercury, due to a decrease of 5.7 mm. in systolic pressure and an increase of 5.4 mm. in diastolic pressure. In table 2 the lowering of the postexercise pulse pressure is apparently due both to a lowered basal pulse pressure and a decrease in the pulse pressure response to stress.

Bohn[23] reported a marked fall in the diastolic pressure following moderate physical exertion, and emphasized this as an important diagnostic sign. Examination of the data of individual cases did not confirm this finding. However, the conditions of exercise were different in the two studies. Burchell and Wood[24] found no diagnostic changes in the blood pressure during or after exercise when the pressure was directly recorded.

Some reliance is placed by clinicians on an increased pulse pressure as an auxiliary clinical sign helpful in the diagnosis of patency of the ductus, and it is thought that relative increase of the pulse pressure and especially a low diastolic pressure is a clinical index of the size of the ductus and gives an estimation of the arteriovenous flow. The situation would appear to be analogous in many respects to aortic regurgitation of valvular origin, where increased pulse pressure tends to parallel the degree of regurgitation. In aortic regurgitation reflux flow is limited by the diastolic capacity of the left ventricle. However, when the pulmonary vascular bed receives the aortic-pulmonary regurgitation, the capacity of this to receive the reflux flow is great and the flow should always be maximum, limited only by the size and length of the ductus arteriosus and by pressure gradients, and not dependent upon dilatation of a heart chamber.

The good correlation between an elevated pulse pressure and an increase in blood volume, shown in chart 2, suggests a relation of the pulse pressure to the abnormal dynamics of the circulation in the presence of a patent ductus arteriosus.

4. Blood Gases and pH_s: The average arterial oxygen saturation of 95.4% in 23 cases of patent ductus arteriosus preoperatively is similar to the average of 95.7% in 39 normal children studied by the same method. Of the 23 cases, 17 had saturations above 95%, but 3 had the low values of 92.3, 87.5 and 89.8%. Of 20 cases studied 2 to 3 weeks after closure of the ductus, 17 had a lower saturation than the preoperative value. The mean difference, 2.3% units, is statistically significant, for $t = 3.6$, and $P = 0.01$. Of 7 cases studied several months after closure, 3 had an oxygen saturation below 93%.

These observations may be interpreted either as the result of pulmonary disturbance due to the surgical procedure, or resulting from a minor degree of pulmonary insufficiency, existent preoperatively but masked by the effects of recirculation of blood through the lungs. With the information available, it is impossible to arrive at the true explanation, but the following evidence should be considered.

The possibility of pulmonary damage is suggested by Maier and Cournand's report[25] of prolonged lowered oxygen saturation following thoracic surgery. The circumstances are not comparable, however, and pulmonary damage due to surgery does not seem probable. The patients in this group undergoing surgery were well and active both pre- and postoperatively, in most cases capable of undertaking normal activity, and chest fluoroscopy or roentgenograph showed no discernible pulmonary abnormality. It was not possible to obtain a comparable control series of surgical cases since thoracotomy usually is not done without additional pulmonary surgery.

Preoperative arterial saturations of 87.5 and 89.8% in two cases of patent ductus arteriosus are evidence that in these two cases pulmonary insufficiency existed before operation. Other cases have been reported in the literature with evidence of pulmonary hypertension and histologic changes in the pulmonary vascular bed.[26-28] In the face of normal arterial saturation in the majority of patients with a patent ductus arteriosus it must be assumed that if vascular changes impeding oxygen diffusion are common, they are ordinarily minor in degree and are masked before surgery by the effects of recirculation. Circulation of arterial blood through the patent ductus raises the oxygen level of blood entering the lung capillaries. It is conceivable that, because less oxygen per unit volume of blood would be required to reach normal arterial saturation, the normal alveolar-arterial pressure gradient for oxygen may be maintained, even though diffusion through the alveolar walls is impaired by the vascular changes.

It is also possible that normal arterial oxygen pressure could be maintained in the presence of impaired alveolar diffusion by raising the alveolar pO_2 level through hyperventilation. Alveolar samples were not analyzed and little data are available on pulmonary ventilation, but the absence of a significant change from the preoperative arterial pCO_2 value in arterial blood samples drawn two to three weeks after ligation suggests that there is no great change in the rate of lung ventilation at that time, consistent with the lowering of arterial oxygen saturation which occurs postoperatively.

In the majority of cases of patent ductus arteriosus the existence of impaired diffusion due to vascular changes resulting from excessive pulmonary flow must remain hypothetic, for the present, at least. The report of Parker and Weiss[29] relative to pulmonary changes in the presence of chronic congestion due to an obstructive mitral lesion does not seem applicable to a situation where pulmonary flow is increased but where obstructive congestion is absent. Benditt[30] examined sections of lung in 10 cases of patent ductus arteriosus where pathologic material was available from the presurgical era, and found no unequivocal evidence of vascular changes in sections stained with H and E. Blalock[31] also found no changes in the pulmonary vascular system in dogs who had an artificial surgical ductus for a period of five years. Dry, Harrington and Edwards[32] found no remarkable changes in the alveolar walls in a 25 year old patient who had a ductus ligation 4½ years earlier, even though the patient had evidence of continuing cardiac distress and coexisting auricular fibrillation. In spite of evidence to the contrary, the consistent decrease in arterial saturation following ligation of the ductus would seem to require further studies with special stains before the possibility of changes sufficient to interfere with oxygen diffusion can be dismissed.

The CO_2 tension of arterial blood in individuals with a patent ductus arteriosus tends to be lower than normal. The average for 23 cases is 35.0 mm. as compared with the averages of 38.0 mm. for normal children aged 10 to 12 years, 41.5 mm. for normal boys 13 to 17 years, and comparable values in the literature.[33-37] The two to three weeks postligation pCO_2 values of arterial blood were higher than before surgery in only one half the cases and the average of 34.3 mm. after ligation is not significantly different ($t = 1.5$) from the preoperative average of 34.6 mm. for the same individuals. On the other hand, the average of samples drawn 2 to 10 months postoperatively was 38.5 mm., which is 2.2 mm. higher than the average of corresponding samples examined before closure and close to the average for normals. The results suggest a tendency toward hyperventilation in

patients with a patent ductus arteriosus. If this is so, it must be assumed that normal lung ventilation returns slowly and is unrelated to the decrease in arterial saturation which appears within two to three weeks after closure of the ductus.

The pH_s values were slightly high preoperatively, with an average of 7.419. Postoperatively two to three weeks the average was 7.434, but several months later the average was 7.393, which is close to the normal level. The elevated pH_s values are probably related to the lowered CO_2 tension.

The CO_2 combining power of the arterial plasma tends to be raised slightly in samples drawn two to three weeks after closure of the ductus. This change occurred in 17 of the 20 cases studied. While this change was slight in most cases, in a few cases it was very large. The average increase of 2.10 volumes per cent would seem to be significant, for $t = 2.7$ and $P = 0.02$. Such a change would appear to be temporary, since in 5 of 7 cases studied at a later period the CO_2 combining power was slightly lower than it was preoperatively. The increase in CO_2 combining power in the absence of change in CO_2 tension would suggest a retention of fixed base during the recuperative postoperative period. Preoperative values of CO_2 combining power for individuals with a patent ductus arteriosus fall within the normal range of variation.

Summary

The effect of the patent ductus arteriosus on the circulation and on the arterial blood gases and pH_s has been studied. The pulmonary blood flow diminished 19.6 to 61.8% following ligation in 12 cases examined. The blood volume diminished following closure of the ductus in most cases. Likewise, the heart rate lessened and the pulse pressure was lower after surgery. Arterial oxygen saturation was low preoperatively in some cases and in most instances postoperatively, and this low value sometimes persisted. Some aspects of the data presented have been discussed in detail.

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SPANISH ABSTRACT

Los Efectos de la Persistencia del Conducto Arterioso Sobre la Corriente Sanguinea Pulmonar, Volumen Sanguineo, Frecuencia Cardiaca, Presion Arterial, y Gases y pH de la sangre arterial

Los efectos de la persistencia del conducto arterioso en la circulación y en los gases y pH de la sangre arterial fueron estudiados. La corriente circulatoria pulmonar disminuyó (19.6% a 61.8%) siguiente a la ligadura del conducto en doce casos examinados. El volumen sanguineo disminuyó en la mayoria de los casos siguiendo a la ligadura del conducto. Asimismo, la frecuencia cardiaca y la presion del pulso fué mas baja después de la operacion. La saturacion de oxigeno de la sangre arterial estuvo disminuida en algunos casos antes de la operacion asi como en la mayoria de los casos post-operados, en los cuales a veces esta valor bajo de la saturacion de oxigeno persistió por un tiempo. Los autores discuten detalladamente varios aspectos de los datos presentados.

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SITUS INVERSUS, BRONCHIECTASIS AND SINUSITIS

Report of a Family with Two Cases of Kartagener's Triad and Two Additional Cases of Bronchiectasis Among Six Siblings

By W. H. BERGSTROM, M.D., C. D. COOK, M.D., J. SCANNELL, M.D., AND WILLIAM BERENBERG, M.D.
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KARTAGENER[1] in 1933 reported four cases of concurrent bronchiectasis, sinus inversus and sinusitis, a triad which now bears his name. Isolated instances of the syndrome had previously been reported by Siewert[2] and by Gunther.[3] Up to the present, 80 such cases have been recorded although in only 16 of these has clearcut roentgenographic evidence of bronchiectasis been presented. The 80 cases are summarized briefly in table 1.

The coincidence of bronchiectasis and situs inversus—borne out by surveys[4-7] which demonstrate that bronchiectasis occurs in 12 to 23% of cases of transposition of the

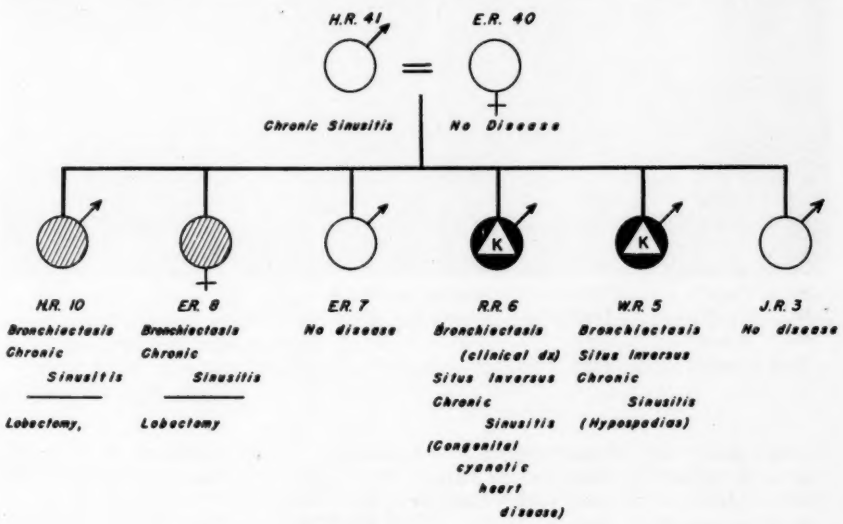

CHART 1. Diagram of R. Family.

viscera—supports the hypothesis advanced by Kartagener and others that hereditary predisposition may be a determining factor in certain cases of bronchiectasis. This would appear to be true in the family that is the subject of the present report. Of this family of

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TABLE 1

COLLECTED CASES OF KARTAGENER'S SYNDROME

	Author	Year	Cases	Age at Onset	Age Seen	Sex	Family History
1	Siewert[2]	1904	1	Infancy	21	M	?
2	Oeri[14]	1909	1				
3–4	Gunther[3]	1923	2	?	?	F, F	Siblings
5–8	Kartagener[1]	1933	4	6 mo.	14	F	? Mother (affected—lungs)
				Childhood	27	F	?
				20 yr.	32	F	Neg.
				Infancy	26	M	? Mother, ? nieces and nephews
9–10	Nussel[15]	1934	2	Infancy	13	M	?
				2 yr.	14	F	?
11	Behrmann[16]	1935	1	12 yr.	21	M	Neg.
12–13	Kartagener[8]	1935	2	5 yr.	32	F	Siblings
				?	?	F	
14–19	Kartagener[7]	1935	6	59 yr.	58	F	?
				Childhood	19	F	?
				12 yr.	34	M	?
				?	28	F	?
				?	32	M	?
				Infancy	26	F	?
20–24	Adams and Churchill[5]	1937	5	54 yr.	9	F	?
				20 yr.	22	M	?
				Childhood	23	F	?
				20 yr.	28	F(Negro)	?
				Infancy	22	M	?
25	Glaum[17]	1938	1	1 yr.	17	F	Neg.
26–27	Cockayne[11]	1938	1	?	?	M	Sister with situs inversus totalis
27	Rosenthal[18]	1939	1	8 yr.	28	M	Neg.
28	Nagy[19]	1940	1	Infancy	8	F	?
29	Cole[20]	1940	1	Infancy	22	M	?
30	Adland[21]	1941	1	3 yr.	11	F	?
31–34	Lopez[9]	1944	4	?	?	M	Siblings
				?	?	M	
				?	?	F	
				?	?	?	
35–48	Olsen[4]	1943	14	?	Survey		Not given
49	Richards[22]	1944	1	3 days	?	M	Neg.
50	Delp[23]	1946	1	Childhood	22	M	?
51–52	Russakoff[10]	1946	2	?	34	M	Neg.
				?	7	F	?
53–80	Torgerson[6]	1947	28	?	Survey		Not given
81–82	Present Report	1949	2	17 mo.	6	M	Siblings; 2 other siblings had bronchiectasis
				2 yr.	5	M	

father and mother and six children, two siblings presented the picture of Kartagener's syndrome, two had bronchiectasis and sinusitis without dextrocardia and two were normal (see chart 1).

The histories of the individual members of the family follow:

Father: H.R., aged 41 yr., was in good health except for a chronic rhinitis and cough that had persisted since an attack of acute frontal sinusitis at the age of 23 yr. He had been entirely well during childhood and free from respiratory disease. There was no history of chronic pulmonary or cardiac disease among his relatives. Of 8 siblings, 4 were well, 2 had died in infancy and 2 at the age of 30, of causes unknown.

Examination at the clinic at the request of the authors revealed no abnormal physical findings. Roentgen films and fluoroscopic examination of the chest and sinuses were within normal limits.

Mother: E.R., aged 40 yr., had always been well. There was no family history of cardiac or respiratory disease. Four siblings and their children were living and well.

Eldest Son: H.R., aged 10 yr., was admitted to the Massachusetts General Hospital with a diagnosis of bilateral bronchiectasis and sinusitis.

He presented a history of "runny nose" since infancy, frequent upper respiratory tract infections

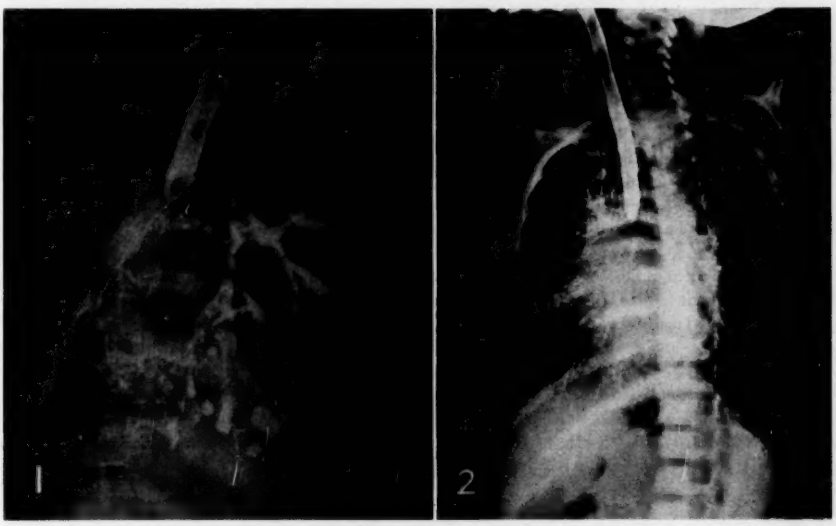

FIG. 1. H. R., eldest boy. Right anterior oblique projection of bronchogram to show extensive bronchiectasis involving entire left lower lobe and both segments of lingula. (Reproduced with the permission of W. B. Saunders Company.)

FIG. 2. W. R., fifth child. Reproduction of bronchogram which demonstrates cylindrical bronchiectasis in left middle lobe.

and cough. At the age of 17 mo. he had had an attack of pneumonia and otitis media. From that time he had an almost constant purulent rhinitis and a chronic cough productive of yellowish sputum, punctuated by several attacks of bronchitis and pneumonia. He had not been short of breath or cyanotic. Physical development had been reasonably normal.

The profuse mucopurulent nasal discharge was obvious at the time of admission. Dullness at the left base posteriorly and moist rales at both bases were noted. Roentgenographic examination of the chest (see Fig. 1) showed collapse of the left lower lobe and the right middle lobe. Bronchography demonstrated bronchiectasis in the corresponding areas. A bronchoscopy showed increased mucopurulent bronchial secretions. A tuberculin test 1-1000 was negative. Vitamin A tolerance test was within normal limits.

Shortly after admission a large nasal polyp was removed and, after a preliminary course of aerosol penicillin and streptomycin, a left lower lobectomy and ligulectomy were performed. The immediate postoperative course was complicated by an abundance of thick, tenacious bronchial secretions, and satisfactory seration of both lungs was achieved with difficulty. The clinical results so far have

been disappointing in that he has continued to have a productive cough and in addition shows some exertional dyspnea and asthenia. His left upper lobe is now extensively involved by a chronic suppurative process.

Pathologic examination of the operative specimen showed a completely collapsed lobe that was thick, edematous and "looked as if it had never been expanded." The bronchi were prominent, dilated and extended almost to the pleural surfaces. The bronchial walls did not appear particularly atrophic; their mucosa was irregularly wrinkled. The microscopic sections were reviewed by Dr. T. B. Mallory. There was considerable variation from bronchus to bronchus in the preservation of epithelium, musculature and cartilage. Islands of scar tissue enclosing epithelial-lined tubes and spaces were evidence of past infection as well as atelectasis; considerable obliterative endarteritis suggested both infection and disuse. In short, the picture was in keeping with the "acquired" type of bronchiectasis.

Final diagnosis: Chronic sinusitis, bilateral bronchiectasis, nasal polyposis.

Eldest Daughter: E.R., aged 9 yr., was first admitted to the Children's Medical Center at the age of 7 yr.

At 11 mo. of age and again at 6 yr., she had an acute middle ear infection. At the age of 4 yr., her tonsils and adenoids had been removed. A second adenoidectomy had been performed at the age of 6¼ yr. Since the age of 5½ yr. she had had a chronic productive cough and persistent purulent nasal discharge.

On admission at 9 yr. of age, the patient was thin but otherwise adequately developed. A profuse mucopurulent nasal discharge was present and slight dullness, decreased breath sounds and rales were noted at the base of the right lung. Bronchograms demonstrated bronchiectasis of the right middle and right lower lobes, with partial atelectasis of the former. Sinus films showed considerable clouding of both antra and the ethmoid cells. A tuberculin test 1:10 was negative.

Several 6 wk. courses of aerosol penicillin and streptomycin were ineffective. Finally, 1 yr. after admission, a right middle lobectomy was performed, followed by marked clinical improvement of the patient. Pathologic report confirmed the diagnosis of bronchiectasis with chronic pneumonitis. No gross definite sacculation of the bronchi was found, but the walls were not firm as normal and the bronchi appeared abnormally large. There was considerable fibrosis in the peribronchial area and the alveolar septa were thickened.

Bilateral nasal polypectomies were performed 14 mo. later for persistent nasal discharge and mouth breathing. At the last follow-up examination 1½ yr. postlobectomy, she was essentially asymptomatic.

Final Diagnosis: Rhinitis, nasal polyposis, sinusitis, bronchiectasis, right middle and right lower lobe.

Third Child: E.R., a 7 yr. old boy, was in apparent good health. On examination at the Children's Clinic of the Massachusetts General Hospital, no abnormalities were detected.

Fourth Child: R.R., a 6 yr. old boy, was admitted to the Children's Medical Center for evaluation of cyanosis persistent since his birth. Since the age of 2 yr., he had had continual nasal obstruction with thick purulent discharge and frequent loose cough. His motor development had been retarded, but mental development was normal. He attended school and played actively with only slight dyspnea. He did not squat. He had no dysphagia, stridor or chest pain.

The patient's cyanosis was moderately severe and his respiration slightly labored. Marked clubbing of the fingers and toes was present. No pulsations in the neck were noted. He had a thick, purulent nasal discharge on the right and coarse rhonchi and crepitant rales were heard at both lung bases. The cardiac dullness extended to the right of the sternum and there was a palpable thrill in the third interspace at the right sternal border associated with a harsh systolic murmur transmitted to the base of the heart and the right clavicle. The second heart sound was loud and snapping. Blood pressure in the right arm was 88/58 mm./Hg, in the left 82/50 mm./Hg. Pulsations in the feet were normal.

Hemoglobin was 16.5 gm./100 cc. Circulation time with decholin was 4 and 19 sec. Electrocardiogram showed inversion of all complexes in leads 1 and 2. Roentgenographic examination of the chest showed dextrocardia, cardiac enlargement, particularly in the region of the left ventricle, and engorgement of the pulmonary vessels. The plain films were suggestive of bilateral bronchiectasis. Angiocardiography demonstrated an enlarged aorta arising on the right and descending on the left. The stomach bubble was on the right, liver dullness on the left. Sinus films were consistent with ethmoid and maxillary sinusitis.

No treatment was given and the patient's condition 5 mo. after discharge remained unchanged.

Final Diagnosis: Chronic sinusitis, situs inversus totalis, congenital heart disease with cyanosis, bilateral bronchiectasis.

Fifth Child: W.R., a 5 yr. old boy, was admitted to the Massachusetts General Hospital with a diagnosis of otitis media of 3 wk.' duration. Since the age of 2 yr. the child had had an almost constant nasal discharge and loose cough. His symptoms were intensified by frequent colds. He had had no dyspnea or cyanosis.

A perforation of the left ear drum was noted on admission. Coarse breath sounds, scattered rhonchi and bubbling rales were heard over both lung fields. Cardiac dullness lay to the right of the sternum and the apical impulse lay in the right fifth interspace. The heart was not enlarged and the sounds were normal. Liver dullness was percussed to the left and gastric tympany to the right. Mild hypospadias was present. Plain films of the chest, confirmed by bronchography, demonstrated bronchiectasis and collapse of the left middle lobe (see Fig. 2).

Cardiac shadow and aorta lay on the right. Sinus films revealed pansinusitis. ECG was consistent with dextrocardia, but otherwise normal.

Penicillin therapy resulted in clearing of the middle ear infection but had no apparent effect on the bronchiectasis. Aerosol therapy was technically impossible. Patient was discharged to the Children's Medical Out-Patient Department at his mother's request, since at that time she had 3 other children hospitalized and the child's problem did not seem urgent.

Final Diagnosis: Bronchiectasis, left middle lobe, pansinusitis, situs inversus totalis.

Youngest Child: J. R., a 3 yr. old boy, had always been entirely well with no history of chronic respiratory tract disease. When examined in the Children's Medical Out-Patient Clinic, Massachusetts General Hospital, no abnormalities were noted.

Discussion

Four members of the family here reported had clinical bronchiectasis of the so-called acquired type with symptoms that began in early childhood. In all four, profuse nasal discharge was a prominent feature. Two of the four had complete transposition of the viscera as well, and these two had additional anomalies: one, hypospadias; the other, congenital heart disease with cyanosis. No history of complicating infectious disease during any pregnancy was obtained from the mother. Two siblings had bronchiectasis that required lobectomy. Two siblings were healthy and the traceable family presented no significant history of respiratory tract disease.

Among the previously reported cases of Kartagener's triad, there are three families in which more than one member was so afflicted. Gunther[3] reported two sisters among four siblings. A parent, five aunts and an uncle were all free of the disease. Kartagener[8] reported two sisters with the triad and a brother normal except for epilepsy. Lopez[9] found two brothers and a sister with situs inversus, bronchiectasis and sinusitis. The present investigators have found no previous report of the multiple occurrence in a single family of Kartagener's triad plus bronchiectasis in other members.

Torgersen[6] reports a 25% incidence of bronchiectasis and nasal polyposis among 77 siblings of 28 persons with Kartagener's syndrome, while among 496 siblings of 93 persons with situs inversus alone, he found only three nasal polyps and none with bronchiectasis. These findings are illuminating in view of the inference which can be drawn from frequency statistics that certain persons with situs inversus may have a genetic predisposition to bronchiectasis. Situs inversus occurs in approximately one in 8000 persons.[3,5,6,10] Bronchiectasis is found in from 12 to 23% of persons with situs inversus, but in only .3 to .5% of the general hospital and clinical population.[4,5] It is of interest that such a genetic predisposition to bronchiectasis is not manifest in the siblings of persons with situs inversus alone, although strikingly so in the siblings of 28 persons with Kartagener's

triad. This apparent genetic difference between situs inversus alone and situs inversus-bronchiectasis-sinusitis would support the suggestion of Adams and Churchill[5] that situs inversus may result either from a mutation affecting the genetic composition of the zygote, or from environmental influences acting prior to or during the earliest stages of cell division. It is of interest to note Olsen's report[4] of 11 of 85 patients with situs inversus who had additional anomalies, including congenital heart disease, hydrocephalus, imperforate anus, cleft palate, flail thumb and accessory digits. Cockayne[11] found among 55 unselected cases of situs inversus five with congenital heart disease, and lists from the literature 40 cases of such association, including 15 with a diagnosis of tetralogy of Fallot. That Kartagener's syndrome is a pediatric problem is shown in table 2. Approximately 90% of the cases in which details as to age at onset of symptoms were given began at 14 years or under.

It seems not unlikely that the combination in a single family of two siblings with Kartagener's triad and two with bronchiectasis alone may be the result of the same unknown

TABLE 2

AGE INCIDENCE AT ONSET OF SYMPTOMS IN KARTAGENER'S SYNDROME

2 yr. and under	13
2 to 14 yr.	10
14 yr. and over	3
Age not reported	55

mechanism that is responsible for the familial instance of monstrosities. Indeed, Adams and Churchill have pointed out that it is logical to regard persons with Kartagener's triad as monsters in a technical sense. This concept gains support from the fact that four family groups, including the one here reported, have shown multiple occurrences of Kartagener's syndrome, whereas in only two instances[1] has there been any suggestion of bronchial disease in the parents or children of persons with the triad. The horizontal distribution observed, therefore, suggests an environmental factor active at the start of embryonic life, rather than a genetic factor which should, if present, become apparent in more than one generation. However, the extent and number of family histories available do not justify any conclusion on this point.

It does seem reasonable to conclude, however, that such cases of bronchiectasis are the result of antenatal influences, whether this be genetic or environmental. Whether this congenital abnormality be an actual structural defect, a physiologic failure of the respiratory epithelium, or a predisposition to infection, cannot be answered on the basis of the evidence here presented. Churchill[12] has recently proposed that an altered secretory activity of the bronchial mucous membrane may constitute the basic abnormality that predisposes to the development of the bronchiectasis. Examination of the resected specimens in the patients reported here failed to disclose unusual pathologic features and the bacteriologic studies revealed nothing of significance. The profuse nasal discharge present in the four children had always a certain element of complicating infection, so that the presence or absence of a primary disturbance of the secretory function of respiratory epithelium could not be determined. The possibility that the relationship between dextrocardia and bronchi-

ectasis may be a mechanical one, i.e., the position of the great vessels may interfere with normal bronchial drainage, remains conjectural. It should be pointed out, however, that stillborn or newborn infants with dextrocardia do not have pathologic changes suggestive of bronchiectasis.[13] In the present series of cases, the segmental pattern of the disease was not out of the ordinary.

Summary

A family is reported in which there occurred two cases of Kartagener's triad and two of bronchiectasis without situs inversus among six siblings. Eighty cases of Kartagener's triad previously reported are tabulated. The relation of this syndrome to the question of the etiology of bronchiectasis is discussed.

Acknowledgment

The authors wish to acknowledge the assistance and suggestions offered by Drs. Allan M. Butler and Charles A. Janeway and roentgenographic intrepretations provided by Dr. E. B. D. Neuhauser.

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SPANISH ABSTRACT

Situs Inversus, Bronquiectasia y Sinusitis; Reporte de dos Casos con la Triada de Kartagener y Dos Casos Adicionales de Bronquiectasia Ocurridos en una Familia de Seis Hermanos

Los autores reportan una familia en la cual ocurrieron dos casos con la triada de Kartagener y dos casos de bronquiectasia sin "situs inversus." Se revisan y tabulan ochenta casos de la triada de Kartagener previamente reportados. Los autores discuten la relacion de este sindrome con el origen etiologico de las bronquiectasias.

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POLIOMYELITIS

Six Year Study of Cases at Children's Hospital, San Francisco

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A PREVIOUS paper[1] presented an interpretation of the clinical deductions based upon the authors' observation of poliomyelitis admissions to Children's Hospital, San Francisco, over a six year period including both epidemic and interepidemic times. It is difficult to establish completely these clinical deductions on a purely statistical basis but the purpose of this paper is to indicate the sources and sampling of the case material and to analyze on a numerical basis some specific observations.

SOURCE OF MATERIAL

Chart 1 represents the occurrence of poliomyelitis in the State of California from January 1, 1943 to November 1, 1949. The lower portion of the chart includes the cases in northern California and the upper part those in southern California. This geographic division of the state is indicated by table 1.

TABLE 1

SOURCES OF CASES (COUNTIES) ADMITTED TO CHILDREN'S HOSPITAL

San Francisco	151	Madera	2
Marin	53	Merced	2
Contra Costa	33	Plumas	2
San Mateo	26	Sacramento	2
Alameda	25	Sutter	2
Solano	24	Tulare	2
Santa Clara	24	Tuolumne	2
Yuba	17	Calaveras	1
Butte	13	Lassen	1
Napa	12	Los Angeles	1
Stanislaus	8	Mariposa	1
Santa Cruz	5	Mendocino	1
Yolo	5	Nevada	1
Siskiyou	5	Riverside	1
Monterey	4	San Joaquin	1
Colusa	2	Tehama	1
Eldorado	2	Non-California	11
Glenn	2		
		Total	453

Epidemic peaks have occurred during the summer months in each of these years, the incidence being particularly great in 1943, 1946, 1948 and 1949. The greatest epidemic

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in the history of the state occurred in 1948. Epidemic peaks are commonly reached in northern California some three or four weeks later than in southern California, this being most readily apparent in a breakdown of weekly incidence.

The number of patients referred from each county to Children's Hospital, San Francisco,

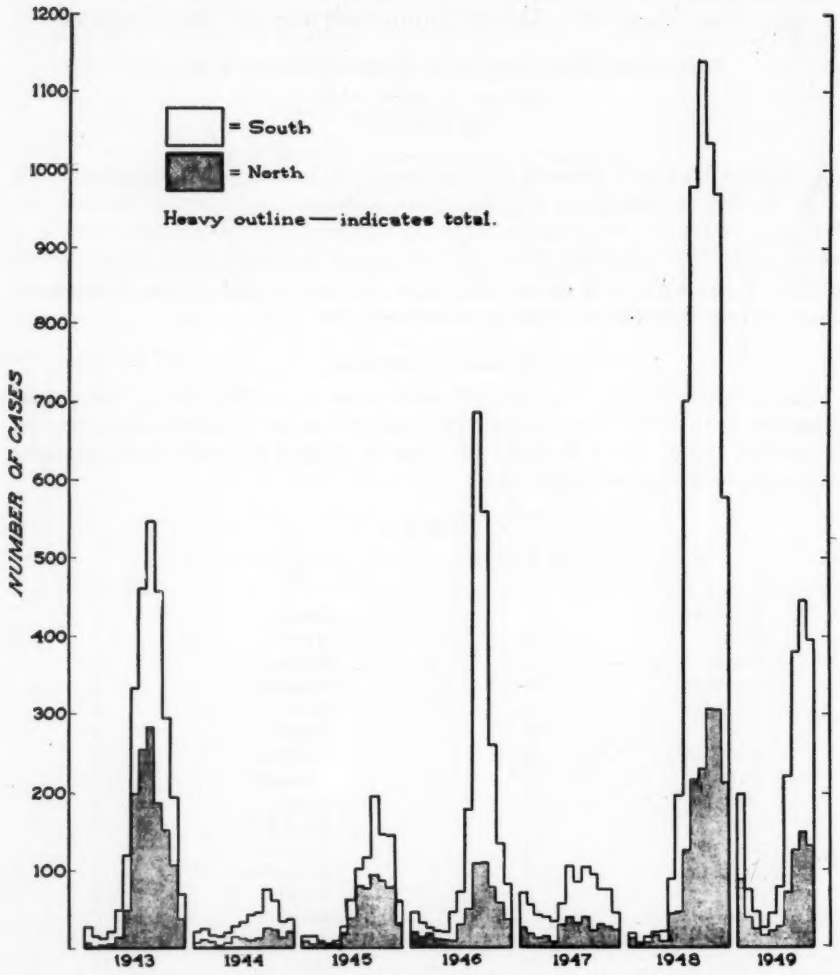

CHART 1. Reported Cases of Poliomyelitis in California—1943-1949.

is indicated in table 1. Many of these counties have either no county hospital or no suitable isolation facilities. Children's Hospital is a private hospital open to all physicians who are members of a county medical society. Except for the communicable disease division, only women and children are admitted but to this latter unit admissions are not limited by age or sex.

This series does not represent a completely valid cross section of the northern California cases. Patients from San Francisco are usually admitted early or on suspicion because the

profession and the public are alerted to this disease. These local cases accordingly include all degrees of severity. The communicable disease division of the San Francisco City and County Hospital accommodates about an equal number of local cases, the difference being largely one of economic status.

The nonlocal cases, on the other hand, represent somewhat more severe ones, especially including more difficult problems in diagnosis and those requiring special methods of treatment, such as artificial respiration, tracheotomy and the care of circulatory failure and urinary retention.

Chart 2 indicates the actual admissions for poliomyelitis from January 1, 1943 to November 1, 1949. The source of these patients covers a wide area so that the epidemic peak consists of a wide plateau which doubtless corresponds to a number of local peaks throughout this region. Admissions are usually at a minimum in March, April and May and are maximal in August, September and October. The severe nature of many of the nonlocal cases contributes to prolonged hospital stay so that there is a lag between admissions and dismissals. Hospital occupancy for this disease during 1949 is indicated by the dotted line on chart 2.

Analysis of Cases

Routine diagnostic procedures are carried out on most admissions. These include blood count, urinalysis, Kolmer and Kahn tests, sedimentation rate and Mantoux test. Spinal puncture is performed on all those admitted early and those admitted later who present diagnostic problems. The spinal fluid is examined for cell count and cytology, culture and animal inoculation when indicated and for quantitative sugar, proteins and chlorides.

Stools have been routinely submitted to the Hooper Foundation for Medical Research for virus isolation although this has actually been done only as occasional sampling. Blood serum samples obtained on admission have been submitted to the Hooper Foundation and to the California State Virus Laboratory for comparative serologic examination in order to exclude from the poliomyelitis series other viral infections of the CNS such as epidemic parotitis, equine encephalomyelitis or lymphocytic choriomeningitis, and this method has been successful in excluding a number of patients in whom the clinical diagnosis was equivocal. Complete autopsy studies were carried out in 21 of 30 fatal cases during 1948 and in 6 or 7 fatal cases during 1949.

Chart 3 is an analysis of admissions by age and sex. Highest incidence in males lay in the age period of 5 to 8 years; in females the highest incidence was at 3 to 4 years. In both males and females the incidence dropped off rapidly after 11 years to reach a low at 19 years. Between the ages of 19 and 30 years the incidence in women is considerably greater than in men. This may be partially accounted for by the fact that the hospital generally serves women and children even though men are admitted to the isolation unit. Also contributing to this higher incidence in adult females is the number of cases in which the disease complicated pregnancy. A study of poliomyelitis and pregnancy carried out with the obstetric department was previously reported[2] as was another study of adult cases.[3]

The admission complaints of 453 consecutive cases are summarized in table 2. These have been grouped with regard to those symptoms referred to the CNS and those referred elsewhere. Obviously these complaints are modified by the stage of the disease at admission and do not represent first symptoms of onset. These do not particularly differ from series reported by many others.

A previous paper expressed the hypothesis that, with the known frequency of exposure

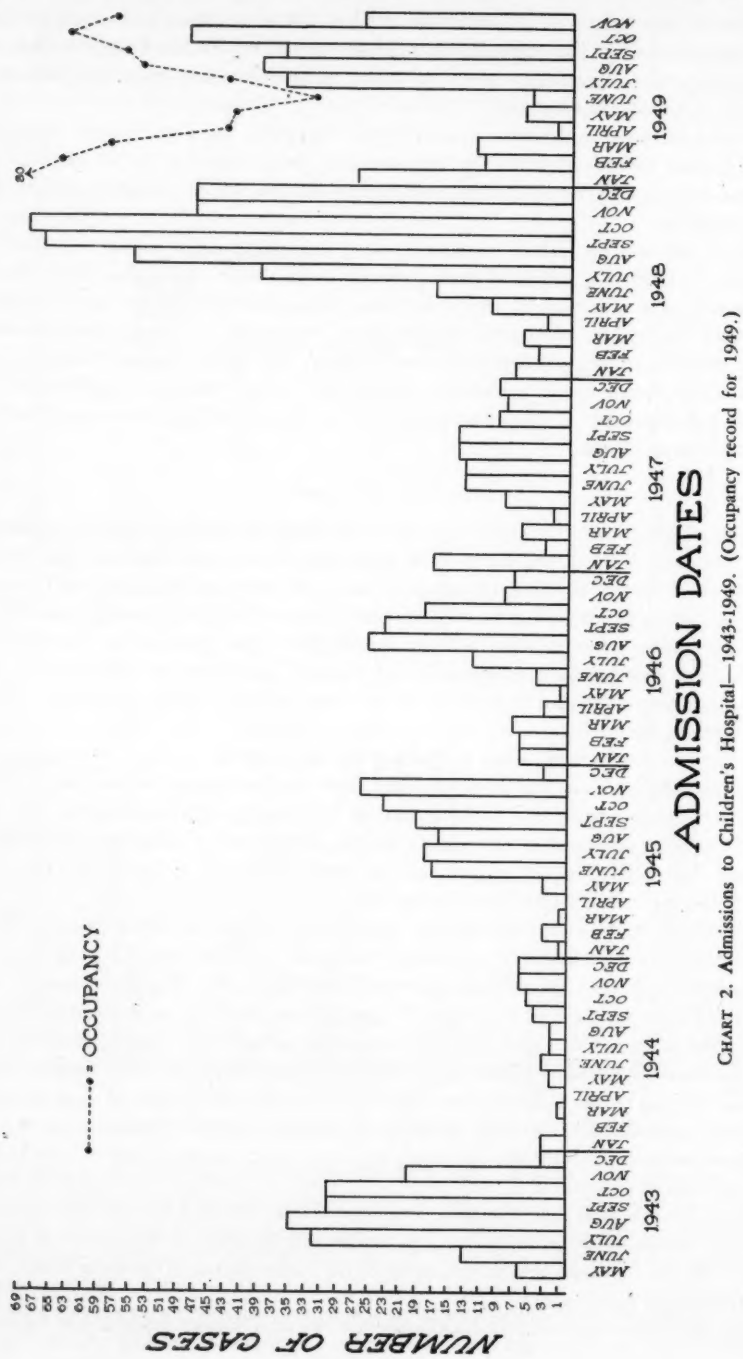

CHART 2. Admissions to Children's Hospital—1943-1949. (Occupancy record for 1949.)

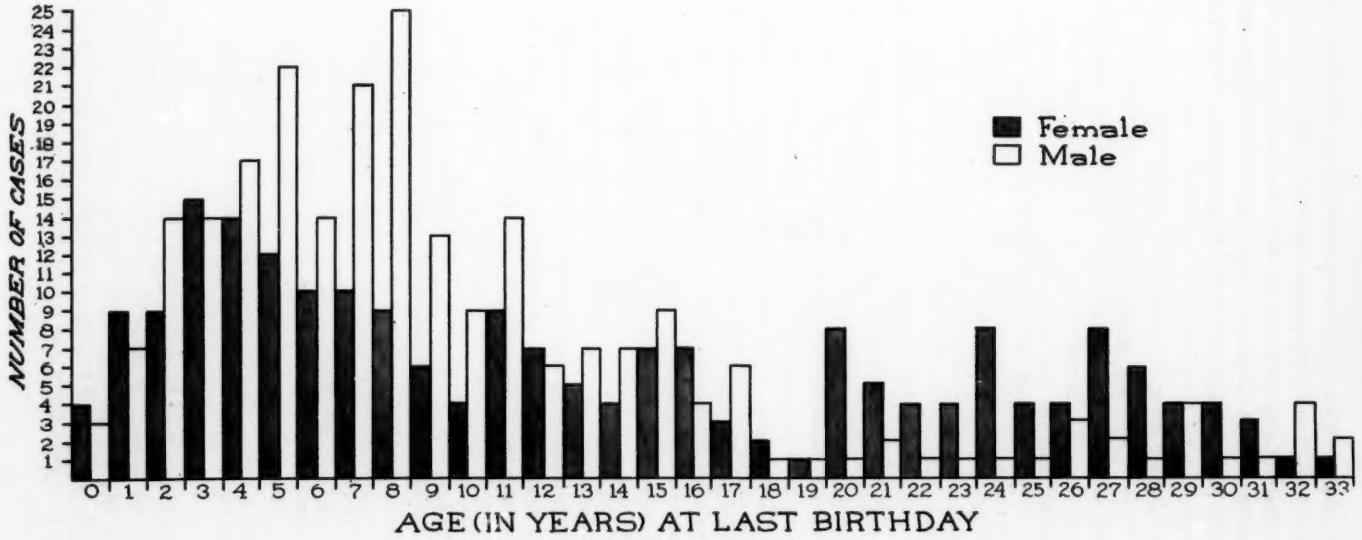

CHART 3. Analysis of Admissions by Age and Sex.

to poliomyelitis, the demonstrable appearance of neutralizing antibodies and the isolation of virus from healthy individuals during an epidemic might be simply indicative of latent infection in which the appearance of evident disease was frequently dependent upon a precipitating traumatic factor. Chilling, fatigue, physical injury, operations and pregnancy have commonly been accepted as favoring or aggravating clinical evidences of this

TABLE 2

CHIEF ADMISSION COMPLAINT

Fever			315
Headache			232
Central nervous system other than headache			338
Stiff neck		186	
Back stiffness		34	
Backache		63	
Neck pain		31	
Changes in sensorium		24	
Irritability	11		
Drowsiness	6		
Dizziness	4		
Convulsions	2		
Coma	1		
Muscle weakness			198
One or more extremities		120	
Inability to swallow		38	
Bladder paralysis		17	
General or misc. muscles		7	
Respiratory		6	
Facial		4	
Diplopia		2	
Nasal voice		1	
Gastrointestinal symptoms			181
Vomiting		114	
Constipation		32	
Nausea		18	
Abdominal pain		13	
Diarrhea		4	
Muscle irritation without weakness			130
Pain in muscles		112	
Twitching of muscles		7	
Stiffness of muscles		6	
Tingling of extremities		3	
Tenderness		2	

disease. To this list the present authors would add the effect of disease due to other infectious agents.

A wide variety of evidences of local or systemic infection have commonly been accepted as symptoms of poliomyelitis virus invasion. Sore throat, tonsillitis, gastroenteritis have been considered by many observers as falling in this category. The present authors challenge this concept as inadequately proved. A far more likely hypothesis is that other infections may serve to convert latent and inapparent infection into obvious CNS disease.

Especially is this true when such infections are accompanied by those objective signs of which poliomyelitis virus would be a most unlikely incitant.

In this series of 453 cases there occurred, five days to one month prior to the onset of CNS symptoms, eight instances of acute contagious disease including rubella, epidemic parotitis, varicella, pertussis and scarlet fever; there were 4 cases of pneumonia and 7 of otitis media. There were 22 instances of preceding mild upper respiratory infection, 9 moderately severe upper respiratory infections and 40 cases with definite objective findings of tonsillar and pharyngeal infections such as follicular tonsillitis. There were numerous cases of gastrointestinal illness, fever, vomiting, diarrhea and abdominal pain occurring 5 to 14 days before the onset of CNS symptoms.

Numerous case histories might be related to support the point of view that unrelated illness may provoke the onset of poliomyelitis. A single one may be used by way of illustration: A woman cared for her child through 6 weeks of mild paralytic poliomyelitis. She then developed a severe diarrhea lasting 3 or 4 days and thereupon developed headache, fever, neck and back stiffness and died 5 days later with universal muscle weakness which included deglutition and respiration.

Many authorities include these evidences of preliminary infection as the initial component of biphasic (dromedary or bactrian) poliomyelitis. This concept appears especially inapplicable to those instances in which preliminary disease differs sharply in symptoms and signs from those evidences of CNS invasion which this virus is known to provoke. The possible etiology of these preceding illnesses must be most carefully studied before they are classed as examples of biphasic responses to poliomyelitis virus. In the series reported here there were only 10 patients with unexplained fever and 11 with miscellaneous complaints which might be regarded as the biphasic course of this disease. In none of these patients was a biphasic course observed in the hospital and it might be noted that this is the usual experience of those who have commented on this biphasic pattern.

It is almost impossible to demonstrate in these patients who have two periods of fever and subjective symptoms the precise point at which poliomyelitis virus becomes the disease-producing agent. The authors' experience strongly supports the view that other illnesses provide a traumatic factor exactly comparable to the recognized influence of physical trauma.

Among these other traumata there were 7 cases which followed recent tonsillectomy and/or adenoidectomy, 6 of which had bulbar involvement. Two followed dental procedures. In one patient a pilonidal sinus had been excised 20 days before admission.

Fatigue as a precipitating cause was noted only when it consisted of competitive athletics, an exhausting swim, a strenuous hike or something beyond the patient's usual tolerance. In a number of patients there was a history of other forms of mechanical trauma, bruises, sprains, falls with sufficient frequency to be persuasive of their etiologic significance. The occurrence of these possible precipitating factors is summarized in table 3.

Treatment

Tables 4 and 5 and chart 4 represent an attempt to analyze the results in cases treated with pooled irradiated plasma. This was given to all patients who were admitted during the febrile period and especially zealously to the ones who had not developed paralysis. Irradiated plasma was used in a dosage comparable to the usual transfusion for the age and weight of the patient. This was repeated once or twice with respect to the clinical course.

As recorded on several previous occasions, the clinical impression that this benefits the outcome has caused the present investigators to continue the practice even though many have abandoned it elsewhere. The use of human plasma at very best employs an agent which is weakly effective in the prevention of sequelae. Any effect may be completely independent of specific immune substances and may be entirely dependent upon partial restoration of the constituents of normal plasma which serve simply to impede invasion of the virus. If normal plasma were an agent of great therapeutic efficacy its value could be easily explored by the use of alternate cases but if its value, even though definite, is slight this could be explored only by an elaborate system of stratified controls in which

TABLE 3

POSSIBLE PRECIPITATING FACTORS

1. Respiratory infections		82
Upper respiratory, simple	22	
Upper respiratory, severe	9	
Tonsil-pharyngeal disease	40	
Otitis media	7	
Pneumonia	4	
2. Gastrointestinal infections		29
3. Fatigue		16
4. Pregnancy		15
1st trimester	7	
2nd trimester	3	
3rd trimester	4	
Postpartum	1	
5. Operative procedures		10
6. Acute contagious disease		8
7. Trauma		6
8. Miscellaneous recognizable infections		11
9. Unexplained fever		10

an attempt was made to correlate age, predisposition, the severity of onset symptoms and duration with the expected outcome. No simple system of alternate cases can provide an easy answer. The authors have particularly avoided comparisons in the paralytic outcome between those patients admitted early in the disease in whom human plasma was employed as a therapeutic agent and those admitted later when there seemed no particular use in administering plasma. In no sense could this latter group serve as a control series for the former group of patients.

Those patients who are admitted early inevitably include a few in whom the diagnosis cannot be unmistakably established and in which the paralytic outcome is unpredictable. Even when the onset symptoms are definitely due to poliomyelitis virus the outcome is variable and completely unpredictable.

Comparisons between early preparalytic cases treated with plasma with the outcome of untreated patients admitted after the appearance of paralysis would unfairly and most mendaciously favor the use of plasma.

Tables 4 and 5 and chart 4 represent an attempt to compare (table 4) the duration of the disease prior to the administration of plasma with the outcome. That this favors the early use of plasma may simply indicate that an early diagnosis makes available the

proportion of nonparalytic outcome which thus weights the results of treatment.

Patients are arranged according to age in table 5. The variation is less striking than the preceding chart although it favors the view that the younger patient given a proportionately greater amount of plasma has a better expected outcome than the adult who, to

TABLE 4

MORBIDITY AND MORTALITY—SERUM-TREATED CASES ARRANGED ACCORDING TO DAY OF SERUM ADMINISTRATION

Day of serum	Paralysis			Died	Unknown	Total	% no residual
	None	Mild	Severe				
1 and 2	41	3	2	2	1	49	83.7
3	42	5	6	5	1	59	71.1
4	16	4	12	3	1	36	44.4
5 plus	18	8	8	4	4	42	43
Total	117	20	28	14	7	186	62%

TABLE 5

MORBIDITY AND MORTALITY—SERUM-TREATED CASES ARRANGED ACCORDING TO AGE OF PATIENT

Ages	Paralysis			Died	Unknown	Total	% no residual
	None	Mild	Severe				
0–5	27	3	4	0	2	36	78
6–10	42	6	9	3	3	63	66.6
11–15	25	5	3	6	2	41	60.9
16–20	10	2	3	0	0	15	
21–25	6	0	5	0	0	8	50.0%
26–30	3	2	5	3	0	13	
30 plus	4	2	2	2	0	10	
Total	117	20	28	14	7	186	62.9%

be sure, has a somewhat poorer expectancy and is given a proportionately smaller amount of plasma.

Chart 4 records the outcome with respect to both the age groups and the day of disease at which plasma was administered. In this chart a better outcome is indicated in the younger patient who is treated early in contrast to the older patient treated late.

Innumerable variables complicate the analysis of this problem of treatment. A simple controlled study will not give the answer. The authors wish not to overstate the conclusions. These charts serve to support but not to prove the clinical impression.

The administration of plasma sometimes produces a prompt effect which may be particularly observed in the young patient. Fifty-one patients in this series had prompt defervescence after plasma administration succeeded by clinical improvement and little or

no residual paralysis. Some cases, on the other hand, illustrating the unpredictability of outcome, showed temporary improvement but with serious sequelae.

If latent infection is a common clinical reality and some adventitious factor precipitates paralytic phenomena as evidence of a disturbance of host virus equilibrium, the therapeutic

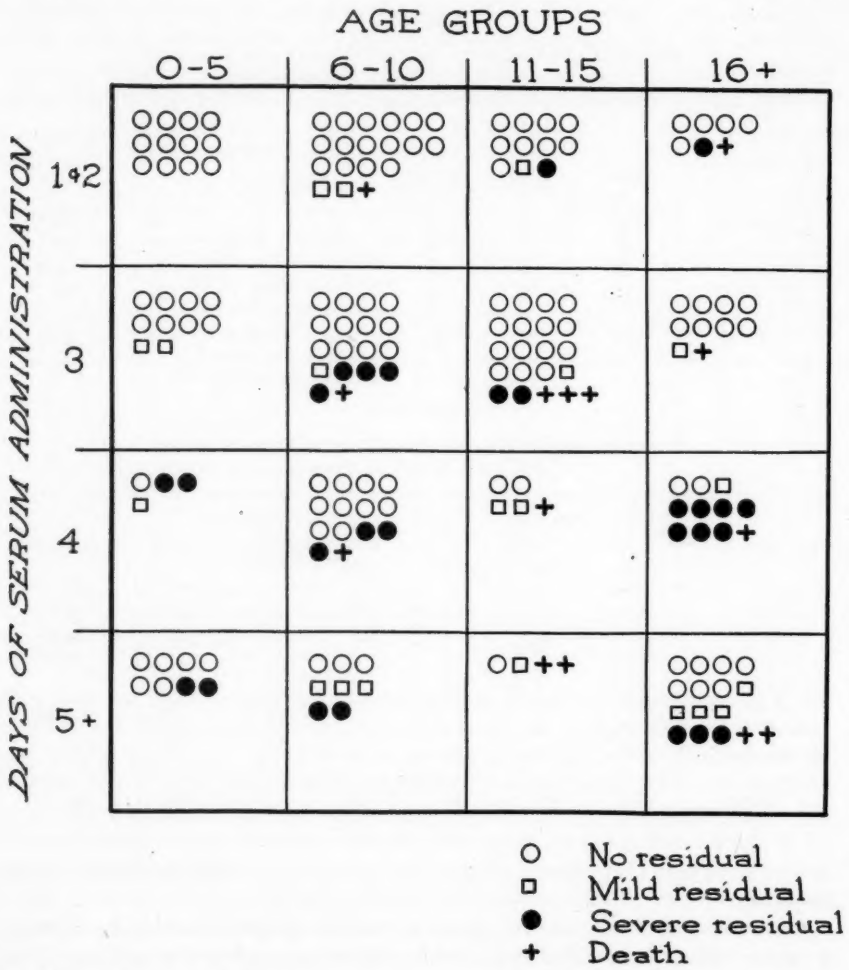

CHART 4. Morbidity and Mortality (arranged according to age and day of administration).

efficacy of plasma may be dependent upon the administration of salts, proteins or of some still unknown factor.

In addition to specific therapeutic agents all the patients have received routine physical therapy. All the patients have been followed through a prolonged period of convalescent care so that various rehabilitating measures could be employed. Patients who are dismissed

as nonparalytic are followed for three years or more to be sure that unnoted muscular weakness or muscle spasm are not responsible for late disability or deformity.

The authors' experience has been that if a diagnosis of poliomyelitis can be acceptably established on the combination of clinical and laboratory findings only a small proportion will completely escape muscular weakness even though this weakness may be transitory and detectable only by careful examination and may recover completely before the end of the two week quarantine period. Frequently, however, the "nonparalytic" case will be one which escapes weakness of the extremities, in which slight degrees of weakness of the muscles of the neck and of the trunk are completely overlooked while the patient is recumbent. Many of these unobserved paralyses will recover spontaneously with ordinary convalescence but some which are early inapparent are the cause of late disability and deformity, such as the progressive scoliosis which may become evident in the growing child.

In the unreliability of the "end point" of infection lies the difficulty of a controlled series which will evaluate a weak therapeutic agent in a disease of variable and unpredictable outcome.

Thus if it is acceptable that the great majority of patients in whom the diagnosis is definitely established early in the infection develop some form of weakness during the period of observation, the efficacy of any form of treatment cannot be successfully investigated by simple comparison of paralytic and nonparalytic sequelae in treated and untreated groups. The value of a weakly effective agent is best made apparent by comparison of the final extent and severity of paralyses in such a controlled series.

Summary

There is presented an analysis of the cases of poliomyelitis admitted to Children's Hospital, San Francisco, during a six year period in an effort to correlate this material with certain deductions regarding course, nature and the factors which affect the outcome.

This series does not constitute a completely valid cross section of northern California epidemics because the admissions were modified by age, economic status, by a somewhat higher proportion of females, and by the fact that, in general, more severe cases were referred to this hospital from outlying districts.

In addition to the physical traumatic factors which are generally admitted to be important in precipitating paralytic poliomyelitis, some evidence is introduced that systemic infections of unrelated etiology may provide a traumatic factor of comparable significance.

In the biphasic febrile course of poliomyelitis the initial period of fever is rarely a matter of hospital observation and proof is usually completely lacking that this initial fever is certainly due to poliomyelitis virus. This preliminary rise in temperature may very well be due to other infectious agents which serve to precipitate the onset of poliomyelitis.

There is much to indicate the considerable ubiquity of poliomyelitis virus among a population during an epidemic. In the absence of great exposure dosage, entrance of the virus into the body may frequently produce inapparent and completely latent infection which may be converted into active disease only by a variety of factors, including unrelated infections, which increase momentarily the susceptibility of the central nervous system of the host.

The value of pooled irradiated human plasma in therapy is admittedly not very great but seems to have a certain value. Statistical demonstration in support of this is almost impossible because of the fact that a weakly effective agent is applied in the treatment of an infection which has an extremely variable outcome.

This measure of treatment may displace the spectrum of outcome favorably without there being a great contrast in the statistical comparison of paralytic or nonparalytic outcome.

Nonparalytic poliomyelitis is generally believed to be of frequent occurrence. Unquestionably this is more frequent with the inclusion of patients in which the diagnosis is based on minimal and unconvincing evidence. If the diagnosis is restricted to those cases with very definite clinical and laboratory findings, only a small proportion will completely escape paralysis though this paralysis may be minimal, may be detected only by careful and repeated examination, and may disappear entirely before the end of the two week period of hospitalization.

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Spanish Abstract

Poliomielitis

Estudio Clinico de los Casos Admitidos al Hospital de Niños de San Francisco Durante un Periodo de Seis Años

Se presenta un análisis de los casos de poliomielitis admitidos al Hospital, de Niño de San Francisco durante un periodo de seis años, con el objeto de comparar este material clinico con ciertas deducciones acerca de curas, naturaleza y factores que afectan al pronostico de la enfermedad.

Los autores indican, qué esta serie no constituye una expresion exacta de las epidemias del Norte de California, debido a que las admisiones de los pacientes fueron modificados por la edad, condicion economica, mayor proporcion de hembras y debido a que los casos mas severos de los distritos suburbanos fueron transferidos a este Hospital.

Se introduce evidencia, que en adicion a los traumas fisicos, estos generalmente aceptados como factores precipitantes de la poliomielitis paralitica, tambien las infecciones sistemicas de etiologia diversa pueden ser factores precipitantes de significancia comparable.

En el curso bifasico febril de la poliomielitis, el periodo inicial febril es raramente un dato de observacion hospitalaria y ciertamente no hay prueba conclusiva que esta fiebre inicial es debida al virus de la poliomielitis. Este aumento preliminar de la temperatura puede ser debido a otros agentes infecciosos, los cuales precipitan el onset de la poliomielitis.

Evidencia clinica indica la ubiquidad considerable del virus de la poliomielitis entre la poblacion durante una epidemia. En la ausencia de un contacto intimo grande, la entrada del virus puede frecuentemente producir una infección inaparente o latente, la cual puede convertirse en la fase activa cuando factores variables, entre ellos infecciones diversas, aumentan momentaneamente la susceptibilidad del sistema nervioso de la persona.

El valor terapeutico del plasma humano irradiado, aunque se admite no muy grande, tiene cierto valor. La demonstración estadistica que asegure este valor beneficioso es practicamente imposible, debido a la naturaleza del agente empleado y al curso extremadamente variable de la enfermedad. Por esa razón es dificil juzgar los resultados del tratamiento, los cuales a veces pueden inclinarse al lado favorable sin haber un contraste grande en la comparasion estadistica de los casos que desarrollan paralisis y los nonparaliticos.

La ocurrencia de poliomielitis sin paralisis es aceptada como frecuente. Sin duda alguna es mucho mas frecuente si se incluyen pacientes en los cuales el diagnostico es basado en evidencia minima o dudosa. Si el diagnostico es restringido a los casos con cuadro tipico clinico y de laboratorio, solo una proporcion ligera de casos escapa completamente los fenomenos paraliticos. Estos ultimos a veces pueden ser minimos, y solo descubiertos mediante examenes cuidadosos y repetidos, y lo que es mas, pueden desaparecer completamente al final del periodo de dos semanas de hospitalizacion.

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EFFECT OF PANCREATIN ON PLASMA VITAMIN A CURVES IN THE CELIAC SYNDROME

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Baltimore

THAT pancreatin improves absorption of natural vitamin A from fish oil in pancreatic deficiency has long been recognized.[1,2] The general benefit which the patient with cystic fibrosis of the pancreas receives from pancreatin has, however, been so much less dramatic than the benefit from the antibiotics that pancreatin has been used with little enthusiasm or omitted by some.[3] The probability remains, however, that in many cases, the most favorable nutritional state, permitting the optimal result from use of the antibiotics, may require enzymatic replacement of the digestive deficiency. The poor experience with pancreatin in the past has been at last partially attributable to poor and variable quality of some of the commercial products.

Improvement of the vitamin A absorption curve by pancreatin† in cystic fibrosis of the pancreas was reported by Clausen, McCoord and Goff,[4] and data on two cases were later presented by McCoord et al.[5] May and Lowe[6] have presented a summary of vitamin A curves with pancreatin‡ in five cases. A huge dose (10 gm.) of pancreatin was used (compared to doses of 0.5 to 5.0 gm. in the present study) and a rise in plasma vitamin A amounting to 42% of the normal rise was found. Believing that pancreatin contained little or no lipase, they tended to attribute the effect to factors other than hydrolysis.

In the present report, vitamin A absorption curves, with and without pancreatin, are presented on each of 33 cases of cystic fibrosis of the pancreas and compared with studies on 15 control patients and 10 with celiac disease. It seemed that comparisons of the curves with and without pancreatin in the same patient might have some usefulness diagnostically and as a guide to therapy. Preliminary report of part of the present study has been made.[7,8]

PROCEDURES USED

The vitamin A was given as halibut liver oil in a dosage of 7000 USP units/kg.§ The test dose of pancreatin was 0.15 gm./kg. as enteric coated granules. One day usually intervened between the days of the tests, the starts of the tests then being 48 hr. apart. The test with pancreatin usually preceded the one without. The doses were given immediately before the early morning meal. The routine vitamin A supplements and pancreatin were omitted on that day or deferred until after the test.

Panteric Granules® were used in the present study and were purchased through or donated by the San Francisco office of Parke, Davis & Co. They were not selected for high enzyme content. The manufacturer's data for these lots show proteolytic activity 225 to 300% USP and amylolytic activity 225 to 300% USP.[9] Lipase activities for these particular lots are not available from the manufacturer, but the process is regulated to satisfy the lipase specification of the British Pharmacopoeia. In determinations by the present investigator, with use of the benzyl butyrate substrate,[10] 1 gm. of the pancreatin used in the present study contained an average lipolytic activity equivalent to

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† U.S.P. Powder, Parke, Davis & Co.

‡ Panteric Granules, Parke, Davis & Co.

§ Parke, Davis & Co., Abbott Laboratories and Mead, Johnson & Co. supplied the halibut liver oil.

approximately 40 ml. of duodenal aspirate. This figure is at variance with a report that 1 gm. of a similar preparation was equivalent to less than 0.2 ml. of duodenal aspirate.[11] (The otherwise puzzling failure of pancreatin to improve fat digestion in pancreatic deficiency in the same report is thus probably explained.) The variations in lipase content may be due to variations in the manufacturing process or to later deterioration.

Diagnosis of pancreatic deficiency depended on duodenal drainage with determination of pancreatic enzymes. An infant-size bilumen gastroduodenal tube was used, the gastric lumen serving to minimize contamination of the duodenal contents by gastric juice.[7,12] Trypsin was determined by the modified method of Anson, by using a buffered substrate of denatured hemoglobin, the tyrosine equivalent of the reaction products being measured by Folin's phenol reagent, with a photoelectric colorimeter. One unit is the amount of enzyme to produce chromogens equal to 1 mEq. of tyrosine/min. at 37.5° under the conditions of the test. Amylase was determined by the modified Willstätter method

TABLE 1

ENZYME CONCENTRATIONS IN DUODENAL DRAINAGE

	Normal Control		Fibrocystic disease		Celiac disease	
	Trypsin*	Amylase*†	Trypsin	Amylase	Trypsin	Amylase
Mean	80	76	0.11	2.7	61	37
Standard Deviation	34	43	0.16	3.3	32	20
Maximum	149	157	0.8	11	125	60
Minimum	26	14	0	0	21	13
No.	18‡	11	32	20	10	9

* The following factors, applied to the tabulated values, give modified Anson and Willstätter u./ml.: trypsin$\times 10^{-4}$, amylase$\times 10^{-3}$.

† Amylase values of infants under 9 mo. of age are normally very low and were therefore excluded from the summary.

‡ Arrangements could not be made to do duodenal drainage on some of the control patients of Fig. 2. Duodenal drainage data from some other control patients are therefore included.

with estimation of the maltose liberated from a buffered starch substrate. The units were obtained by calculation of the reaction constant. The units were expressed per ml. A summary of results of trypsin and amylase determinations in the duodenal drainage is shown in table 1. The cases of cystic fibrosis of the pancreas included in the present report are limited to those in which pancreatic deficiency was of extreme degree, indicated by trypsin concentrations of 0 to 0.8 averaging 0.1. This is in comparison to a range of 21 to 125 averaging 61 in the cases of nonpancreatic steatorrhea and 26 to 149 averaging 80 in controls. Amylase and lipase values were consistently low when pancreatic deficiency was indicated by low trypsin concentrations. Lipase concentrations were normal in celiac disease. Amylase values were also essentially within the normal range in celiac disease but were in the lower part of that range. Vitamin A was determined by the Carr-Price reaction.[13] Determinations were made fasting and at 3 and 5 hr.

RESULTS

The vitamin A studies are presented in charts 1, 2, 3 and 4. The averages of the groups are shown in chart 1. In the control subjects the curves with pancreatin (solid line) and without pancreatin (broken line) are substantially similar. The average fasting levels with and without pancreatin are 43 ± 17* and 46 ± 20 μg., respectively. The 3 and 5 hour averages with pancreatin are 275 ± 75 and 181 ± 70. Without pancreatin they are 234 ± 102 and 231 ± 84. It would seem reasonable to expect that acceleration of digestion by the pancreatin would cause the peak of absorption to come earlier and be higher.

* Standard deviation.

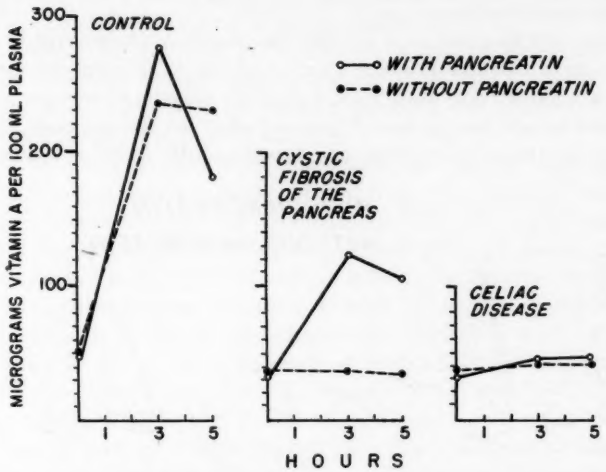

CHART 1. Effect of pancreatin on averaged vitamin A absorption curves of 15 control subjects, 32 cases of cystic fibrosis of pancreas and 10 cases of celiac disease.

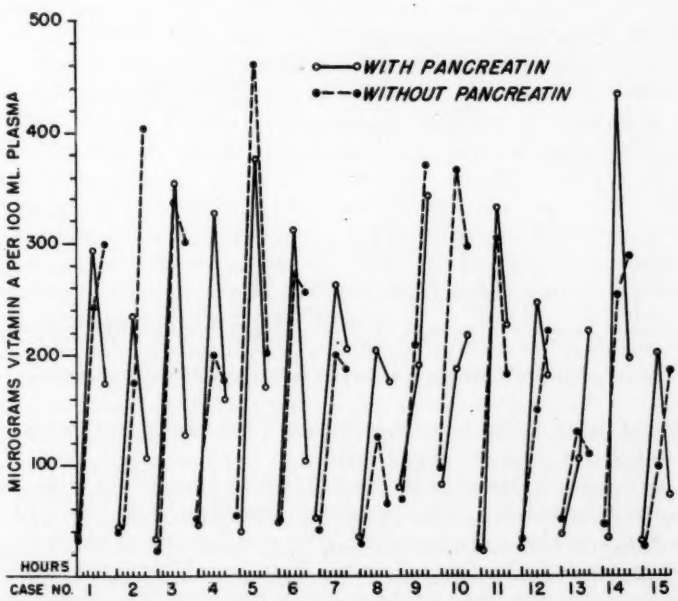

CHART 2. Effect of pancreatin on vitamin A absorption curves of 15 individual control subjects.

Such appears to be the case in the present data although the differences proved to be too small to be statistically significant.

The question may be raised as to whether the vitamin A administered in one test increases the height of the curve obtained in the second test. An investigation of the question in seven subjects showed only a small and statistically insignificant increase in the second curve. McCoord has also noted a lack of "priming effect" on repeated doses.[5] It is not certain, however, that this would apply to subjects with initially depleted vitamin A reserves.

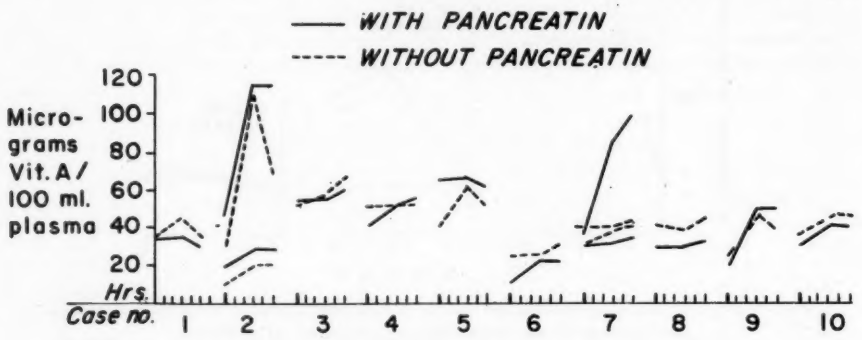

CHART 3. Effect of pancreatin on vitamin A absorption curves in 10 cases of celiac disease.

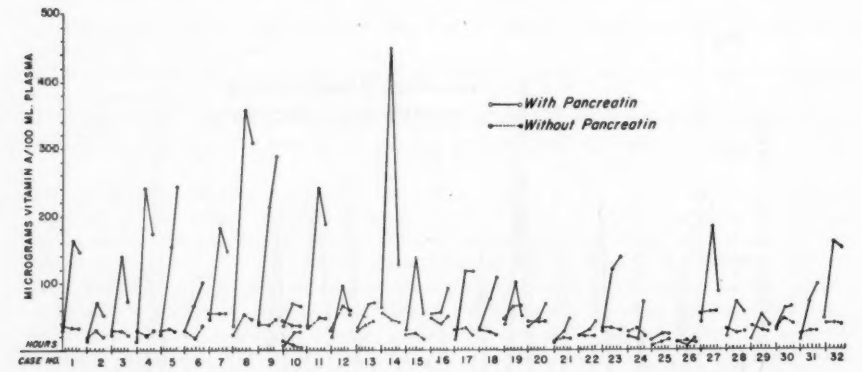

CHART 4. Effect of pancreatin in vitamin A absorption curves in 32 cases of cystic fibrosis of pancreas.

The individual curves of the vitamin A levels at 0, 3 and 5 hours, in 15 control subjects, with and without pancreatin are shown in chart 2.

In the average of 10 cases of celiac disease (chart 1) a normal rise in the vitamin A level failed to occur with or without pancreation. The curves of the individual cases are shown in chart 3. In Case 2, the two upper curves were done after a month of treatment with parenteral crude liver extract and vitamin B complex. Without this medication, the infant had previously been losing weight on a celiac type of formula and the lower set of curves had been obtained. In Case 7, four curves were run, two with pancreatin and two without. The first test done was with pancreatin and was the highest, showing a rise of 60 μg. The later three tests, including another with pancreatin, showed no significant rise.

It seems probable that a fluctuation of the celiac disease occurred between the first two curves, and that the difference was not due to pancreatin.

The vitamin A curves of 32 cases of cystic fibrosis of the pancreas are averaged in chart 1. With pancreatin, the average fasting value was 31 ± 15. At 3 hours the level was 122 ± 95 and at 5 hours 105 ± 70. Without pancreatin the values were 34 ± 12 and the 3 and 5 hour values were 37 ± 15 and 36 ± 15, respectively.

The curves of individual cases of cystic fibrosis of the pancreas are shown in chart 4. Case 2 was a 7 year old boy with history of soft, fatty appearing stools since infancy but no pulmonary symptoms considered significant. He died with gastric hemorrhage and hepatic failure 16 months subsequent to the studies here presented. Autopsy showed only a small fibrous remnant of pancreas with numerous islets. The liver was extremely cirrhotic and showed a microscopic picture similar to the usual "fibrocystic" appearance of the pancreas. There was slight but definite microscopic evidence of involvement of the bronchial tree. Case 10 is a 10 year old boy with history of diarrhea from birth and persistent cough from age of 6 years. He was emaciated and had marked emphysema, loud, coarse, crackling rales, much sputum and clubbing of the extremities. He had been receiving penicillin intramuscularly during much of the previous two years. The lower pair of vitamin A curves was done during the first week of hospitalization. The upper pair of curves was done 6 weeks later, during which time he had received 50,000 to 100,000 μ of vitamin A daily and had received pancreatin and periods of penicillin. The upper pair of curves showed a higher fasting level but essentially no better rise with pancreatin than had been obtained 6 weeks earlier. In spite of the persistence of a low vitamin A curve with pancreatin, this boy gained 6.5 kg. in one year and his respiratory status markedly improved. Case 25 shows essentially no rise with pancreatin. The principal signs in this 4 month old infant were extreme emaciation and a watery steatorrhea. The diarrhea and weight responded immediately to pancreatin with essentially no other treatment. The diarrhea did not recur when a whole milk formula was given with continued pancreatin. A weight gain of 2.5 kg. occurred in 3 months. In spite of this excellent weight gain and administration of massive doses of vitamin B complex, the vitamin A curve with pancreatin has not significantly improved. Case 26 is a 5 year old girl in whom a frank cardiac failure with electrocardiographic evidence of cor pulmonale appeared a few days following this study. This child made a marked improvement upon treatment with digitalis, pancreatin and with penicillin (aerosol and I.M.) alternating with periods of sulfamerazine. Later the penicillin became ineffective but she responded well to aureomycin.

That the curves with pancreatin are generally better in the first half of the series than in the latter may possibly be related to the fact that most of the cases that were tested in outpatient department (5, 8, 16, 18, 20, 21, 22, 23, 24, 25) and were, in general, under less intensive treatment fall in the latter group. Case 8, whose curve, done in the outpatient clinic, was unusually high, was a 4 year old girl who was responding exceptionally well to intensive treatment including penicillin aerosol at home. Most of the fibrocystic patients were on a diet moderately restricted in fat. The tests done on the ward were usually accompanied by lower fat intake than those done in the outpatient department. It seems possible that this may have had an effect which remains to be more fully evaluated.

Discussion

That a high rise in vitamin A with use of pancreatin is not a significant sign regarding ultimate prognosis is indicated by the fact that the two highest and two relatively good

rises occurred among the six patients of this series who have since died (2, 6, 8, 14, 17, 29).

The ages of the patients with cystic fibrosis of the pancreas ranged from 9 weeks to 10 years. In the 12 youngest infants* the average rise in vitamin A with pancreatin was 101. In the 9 oldest children† the average maximum rise observed was 72. The difference may represent the fact that the older children have had more time to develop various pulmonary and gastrointestinal complications. The difference may otherwise be due to greater destruction of the pancreatin in the stomach of the older child.

The occurrence of low vitamin A absorption curves in some newborn infants has been reported.[5,14] This condition, if it was ever present, has apparently not persisted to the ages concerned in the present study, in view of the good rises in the three youngest infants of the control group (chart 2), Cases 5, 11 and 15, aged 7 weeks, 4 months and 3 months, respectively.

The consistent failure of the vitamin A level to rise after halibut liver oil in absence of pancreatin in cases of fibrocystic disease in the present study is striking. The already established diagnostic usefulness of the vitamin A absorption test as usually done without pancreatin is thus illustrated. It should be mentioned, however, that in a lesser degree of pancreatic deficiency in cystic fibrosis of the pancreas, normal vitamin A curves may be obtained without use of pancreatin.[15]

The variability of the rise in plasma vitamin A with pancreatin in fibrocystic disease greatly limits the diagnostic usefulness of the test. It may still be useful in particular cases. There is the advantage that it can be performed with almost no disturbance to the patient (particularly if the vitamin A determinations are done on capillary blood). The diagnostic use is illustrated by the case of a 3½ month old infant first seen with marked cyanosis, cough and emaciation. Since duodenal drainage seemed to be a more disturbing procedure than was justified in view of the condition of the infant, plasma vitamin A levels were determined instead as follows:

Day 1	fasting	45
	3 hr. after halibut liver oil + pancreatin	221
Day 3	3 hr. after halibut liver oil without pancreatin	38
Day 6	3 hr. after halibut liver oil + pancreatin	144
Day 8	3 hr. after halibut liver oil without pancreatin	52

The diagnosis of pancreatic deficiency was thus indicated and was later confirmed by duodenal drainage after improvement had resulted from appropriate treatment.

That the average rise of vitamin A in fibrocystic patients receiving pancreatin falls short of the average normal rise is possibly at least partially attributable to the presence of pulmonary infection[16,17] and other complications, and is not necessarily due to inadequate pancreatic enzyme replacement. The dosage in these tests was approximately twice what is used per meal in the therapeutic routine at this center, with apparently satisfactory effect on the stools, weight gain and maintenance of normal fasting vitamin A levels with use of halibut liver oil as the vitamin supplement.

Question has been raised as to the mechanism of the effect of pancreatin on the vitamin

* No. 3—11 mo.; No. 4—5 mo.; No. 7—5 mo.; No. 11—5 mo.; No. 16—8 mo.; No. 20—7 mo.; No. 23—9 mo.; No. 25—4 mo.; No. 27—8 mo.; No. 28—3 mo.; No. 29—9 wk.; No. 32—4 mo.

† No. 2—7 yr.; No. 8—4 yr.; No. 10—10 yr.; No. 13—4 yr.; No. 18—4 yr.; No. 21—6 yr.; No. 24—5 yr.; No. 26—5 yr.; No. 30—8 yr.

A curve.[6] In view of the lipase content of the pancreatin used, lipolytic action on the vitamin A ester and concomitant fats would seem to provide a reasonable explanation of the effect. The possible occurrence of a special esterase for vitamin A is not to be excluded however.

The present study emphasizes that use of pancreatin in a practical dosage in treatment of cystic fibrosis of the pancreas has a definite effect tending to restore to normal a part of the impaired physiology. The authors have not noticed that pancreatin decreased the appetite more than would seem to be accounted for by the increased efficiency of food utilization. (The practice of giving the pancreatin p. c. may favor this.) As regards cost, the therapeutic dosage of enteric coated granules which are usually given to a 1 to 2 year old infant costs approximately 12 cents daily. The savings in cost of otherwise undigested food probably offset this cost to a substantial degree. As has been suggested,[3] efforts should be made to assure more satisfactory and uniform pancreatic preparations. The variability of the lipase content would probably be decreased were the U. S. Pharmacopoeia to specify a minimum lipase content.

Summary

Vitamin A concentrations of the plasma have been determined following administration of halibut liver oil with and without pancreatin in infants and children. Thirty-three patients with cystic fibrosis of the pancreas were so studied. Without pancreatin the vitamin A concentration failed to rise. With pancreatin (in dosage of 0.15 gm./kg.) an average rise in vitamin A occurred approximating 39% of that found in normal control patients. No consistent effect of pancreatin was found in 10 cases of celiac disease.

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SPANISH ABSTRACT

Los Efectos de la Pancreatina en las Curvas de Vitamina A del Plasma en el Sindrome Celiaco

Las concentraciones de vitamina A del plasma fueron determinadas en lactantes y niños, siguiente a la administracion de aceite de halibut con y sin pancreatina. Asimismo treinta y tres pacientes con enfermedad cistica del pancreas fueron igualmente estudiados. En el grupo sin pancreatina, la concentracion de vitamina A no aumentó. En el grupo con pancreatina añadida (en dosis de 0.15 gm/kg) un aumento promedio de la concentracion de vitamina A ocurrio en un 39% del promedio obtenido en los controles normales. En diez casos con el sindrome celiaco no se encontró efectos consistentes con el uso de la pancreatina.

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DUODENITIS IN CHILDHOOD

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THE occurrence of inflammatory lesions in the stomach and duodenum is relatively uncommon in infants and children. The observation of peptic ulcer in patients of these young age groups has occasionally been reported in pediatric literature but minimal attention has been called to the occurrence of duodenitis in childhood. Judd[1] in 1921 first differentiated between duodenal ulcer and duodenitis; the true ulcer is characterized by a definite crater, an indurated border which is palpable, and hyperemia and stippling of the peritoneal coat. Duodenitis produces hyperemia and stippling of the serosa but the wall is not indurated and on palpation the duodenum is indistinguishable from one that is normal. Examination of the mucosa shows diffuse or local inflammation and occasionally one or more simple erosions.

Boyd[2] noted on histologic studies that the epithelium, while generally intact, was occasionally denuded in a few small areas. Also, the mucosa and submucosa were infiltrated with lymphocytes, plasma cells and occasional eosinophiles and at times the infiltration extended through the muscular layers of the serosa. Konjetzny[3] reported similar microscopic changes in duodenitis, both with and without duodenal ulcer. It was his belief that chronic duodenal ulcer develops on a base of chronic duodenitis. While this view has been opposed by some, Wellbrock,[4] from histopathologic observations, concluded that there is a relationship between duodenal ulcer and duodenitis. The role of duodenitis as it pertains to the development of duodenal ulcer will require further clinical study.

Kirklin[5] in 1929 reported 45 cases of duodenitis found at the time of surgery and in no instance had a preoperative diagnosis been made. He proposed certain roentgenologic criteria essential for the diagnosis. Of prime importance was the markedly increased irritability of the duodenum as manifested by spasticity and hypermotility. Also, the mucosal pattern is commonly coarse and irregularly reticular, there is absence of an ulcer crater and gastric retention is absent or rare. Duodenitis in childhood was first reported in 1935 and the authors noted that while the history and symptoms are not typical in a young patient the roentgenographic findings are similar to those in adults.[6]

In childhood the most prominent radiologic finding of duodenitis is the marked irritability of the duodenal cap noted at fluoroscopy. Little difficulty is experienced in filling the cap but the barium is promptly propelled forward so that the cap is rarely seen fully distended. The radiographs show the reticular appearance due to edema of the mucosa or indentations of the contours resulting from swollen folds seen in profile. The indentations, however, are inconstant and change after each contraction. Because of this variability it is not difficult to distinguish the migrant indentations of duodenitis from the permanent deformities of the cap due to ulcer scars (Fig. 1).

The clinical manifestations in children and adults are in most instances similar, though milder, to those of uncomplicated duodenal ulcer. Occasionally the region concerned

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with maximal complaints is not designated as epigastric in situation, but rather right upper quadrant. In children the ingestion of food and alkalies less constantly relieves the distress in duodenitis than in simple ulcer and a similar observation has been made by Eusterman and Balfour in adult patients.[7] Frequently there is nausea or a distressing fullness in the right upper quadrant occurring shortly after meals and reaching maximal intensity in several hours. Gross hemorrhage occurred in 15% of the adult patients reported by Rivers[8] and occasionally it was the only symptom. Hemorrhage did not occur in any of the children in this report. Vomiting occurs occasionally and night pain is rather

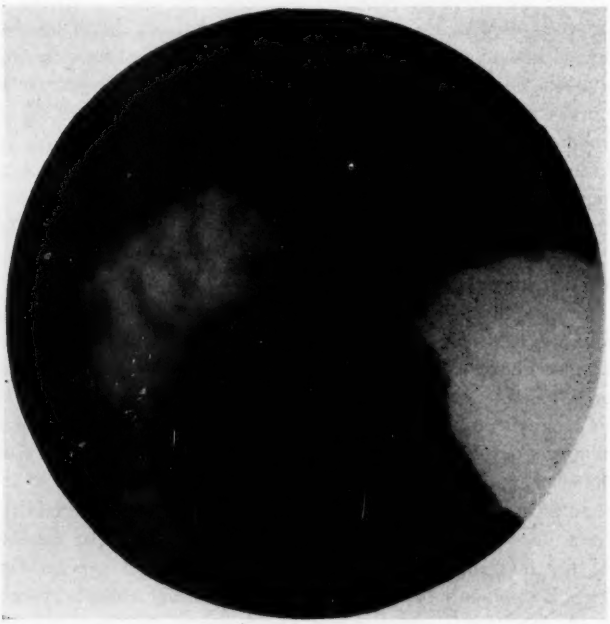

FIG. 1. Radiograph (Case 2) showing marked spasticity of duodenal cap and large mucosal folds characteristic of duodenitis.

frequent in duodenitis of the younger age groups. Pyloric obstruction seemingly does not occur.

Two cases of duodenitis in childhood, each terminating in duodenal ulcer, were observed by Jankelson.[9] He considered that a careful regime of medical management in patients with duodenitis, but without ulceration, might obviate the occurrence of an ulcer.

A group of six children with duodenitis is included in this report. The diagnoses were made roentgenologically from the evidence previously described and all patients were observed within the period 1934-1949. The ages of the children at the time of first examination were 12 years, 6 years, 5 years, 4½ years, 4½ years and 3½ years, respectively. The impression seems warranted that this rarely diagnosed lesion of the duodenum might be found more frequently if the possibility of its occurrence is borne in mind. It is well recognized that adults with peptic ulcer not infrequently give a history of typical ulcer symp-

toms beginning in childhood. The paucity of reports of duodenitis in children indicate that perhaps inadequate attention has been called to the occurrence of this condition in children.

Case Reports

Case 1. B. W., female, aged 12 yr., was first examined because of epigastric discomfort of 8 mo.' duration. The pain, relieved by soda bicarbonate and magnesia magma, usually occurred at night and was of sufficient severity to awaken her. Vomiting had occurred on 1 occasion.

Past history was negative except that she was a nervous, tense child and was occasionally constipated.

Physical examination was noninformative and the fluoroscopic and roentgenographic observation of duodenitis was the only significant laboratory finding.

Treatment consisted of bed rest, sedatives, antispasmodics, alkalies and a modified ulcer diet with milk and cream between meals. Response to therapy was gratifying and within a few weeks she was free of abdominal distress. On examination 2 yr. subsequently she reported there had been no recurrence of the symptoms.

This patient was reported by 1 of the authors (J. B. G.) in 1935.[8]

Case 2. R. T., male, aged 6 yr., had been observed at the clinic since birth. The past medical history was irrelevant except that he was a nervous, high-strung child who suffered from an allergic dermatitis each summer. Two days prior to examination he vomited and complained of severe epigastric pain. The pain was intermittent, awakened him at night, and had no apparent relationship to meals. The vomiting ceased after 24 hr. but the pain persisted.

Physical examination revealed a well developed boy who did not appear acutely ill. Rectal temperature was 37°C. The significant findings were a palpable liver and slight tenderness in the epigastrium and right upper quadrant. A bland diet and sedation were prescribed. During the following week the epigastric pain continued to awaken him at night and was of sufficient severity to necessitate codeine on several occasions. He was admitted to the hospital after 10 days because of the persistent abdominal pain. Laboratory studies were noninformative except for the characteristic fluoroscopic and roentgenographic findings of duodenitis.

A bland diet and antispasmodics before meals were prescribed and the symptoms promptly subsided; 2 mo. later he was without complaints. This patient was followed for the succeeding 2 yr. and symptoms did not recur.

Case 3. L. H., female, aged 5 yr., was first examined because of epigastric pain of 3 or 4 mo.' duration. The pain occurred intermittently throughout the day and was particularly severe at night. There was occasional vomiting, but acid eructations had not been noted. She was chronically constipated and suffered repeated attacks of urticaria though urticaria had not been present for several months prior to examination.

Physical examination was essentially negative, and the only significant laboratory study was fluoroscopic and roentgenographic evidence of duodenitis.

Therapy consisted of a bland diet, alkalies, antispasmodics and sedatives. The symptoms were relieved within a few weeks and in the subsequent 3 yr. there was no recurrence.

Case 4. W. R., male, aged 4½ yr., complained of abdominal pain of 8 mo.' duration when first examined. The pain occurred before meals and during the night. He was a tense, high-strung child and as an infant had been treated for allergic dermatitis. Physical findings were unimpressive and the laboratory studies were essentially normal except for roentgenographic evidence of duodenitis.

Therapy consisted of a bland diet with milk and cream between meals, antacids, antispasmodics and sedatives. Improvement was marked within a few weeks although abdominal discomfort has continued from time to time ever since. Re-examination roentgenographically 3 mo. later showed less irritability of the duodenal cap but a slight deformity at the base of the inferior border of the cap was noted. This was interpreted as an ulcer by the roentgenologist. Similar studies 5 mo. later, however, were negative for evidence of duodenitis or ulcer.

There was recurrence of the symptoms 3 yr. subsequent to the initial examination. Roentgenologic studies demonstrated recurrence of duodenitis and an ulcer regime with appropriate diet and medication was resumed. For the 2 yr. preceding upsetting emotional factors had existed in the patient's home. The father had been under constant observation by a psychiatrist and the mother presented many emotional disturbances and became unduly disturbed over the welfare and health of her

children. Fluoroscopic evidence of duodenitis was still present the year following this second admission.

Case 5. P. B., female, aged 4½ yr., was examined because of chronic cough and episodes of vomiting after meals. The cough had been present for 3 mo., and the vomiting had occurred intermittently for the same period; apparently, vomiting was not precipitated by the cough.

Physical examination revealed a well developed and nourished child. The significant physical findings were mild ichthyosis and a purulent postnasal drainage. Roentgenologic studies of the chest showed increased hilar markings and fluoroscopic and roentgenologic studies of the stomach and duodenum demonstrated duodenitis.

Without specific therapy the symptoms disappeared within a few weeks and during the past 8 mo. have not recurred.

Case 6. G. Q., female, aged 3½ yr., came to the clinic with the complaint of severe abdominal pain of 3 wk.' duration. The pain awakened her at night and was occasionally relieved by taking soda bicarbonate. Vomiting and melena had not occurred though constipation had been noted for the week previous to examination.

Past medical history revealed a known allergy to eggs and milk as an infant.

Physical examination revealed a well developed, highly irritable child. A maculo-papular rash was present on the chest, abdomen and face; hypotonia, profuse perspiration and a moderate erythema of her hands and feet were noted. Blood pressure was 120/80 mm.Hg. Laboratory examination was noninformative except that fluoroscopic and roentgenographic studies showed duodenitis.

The diagnoses were duodenitis and acrodynia. Therapy for the duodenitis consisted of a modified ulcer diet, alkalies, antispasmodics and sedatives. The abdominal complaints promptly subsided and after 2 mo. of continuous therapy symptoms did not recur. The symptoms of acrodynia subsided more slowly, but recovery was apparently complete at the end of 4 mo.

She has been observed at intervals over the past 14 yr. and there has been no recurrence of symptoms.

Comment

The presence of duodenitis can only be suspected clinically; the actual diagnosis depends on roentgenologic or surgical confirmation. From the clinical standpoint the existence of such a lesion may be suspected from the presence of persistent ulcer-like symptoms and chronic or recurrent digestive symptoms which justify roentgen examination of the gastrointestinal tracts of children.

The single symptom quite consistently present in duodenitis of childhood is epigastric pain and this was present in five of the patients. The occurrence of night pain was frequent and relief by food and alkalies was observed occasionally. Vomiting was reported in four patients and a history of constipation was obtained in several instances. Frequently it was difficult to elicit a clearcut description of symptoms from these small patients.

There was a history of allergy in four patients and of interest was the observation by both parents and examiner that three were tense, high-strung and emotional. Whether allergy and a nervous diathesis are coincidental or real factors in the development of duodenitis in children could only be established by observations on a much larger group. Wellbrock[4] and Lipschutz[10] have discussed the part allergic reactions may play in inflammatory lesions of the duodenum. Two children had severe associated illnesses, one had a chronic respiratory infection and the other acrodynia.

Peptic ulcer was suspected in several of the children prior to roentgenographic examination. The diagnosis in each patient was made roentgenologically and in most instances roentgen studies of the stomach and duodenum were repeated.

Response to therapy with a modified ulcer regime and appropriate medications was prompt in five instances. One child (Case 5) recovered without specific therapy; her presenting complaint was vomiting and she had no epigastric distress. Only one child

(Case 4) has suffered recurrence of the symptoms of duodenitis and in this patient roentgenographic evidence of duodenitis was present for a four year period. On one occasion there was fluoroscopic evidence of duodenal ulcer and he is regarded as having had both conditions. The severe psychologic and emotional disturbances in this patient's home are probably major factors in the failure of the duodenal lesions to heal promptly. At present he is improved following psychiatric therapy of both parents. The coexistence of duodenitis and duodenal ulcer has been observed frequently, both roentgenologically and at surgery, in adults.

Duodenitis presents many difficulties concerning its establishment as an entity, concerning its relation to the presence of an ulcer, and concerning the significance as a precursor of an ulcer. Nevertheless, it is likely that any ulcer may have begun as a region of inflammation; also, some reactions of inflammation have not resulted in ulcer but have persisted in the form of diffuse processes which may be termed duodenitis.

In the 15 year period in which the group with duodenitis was observed, a diagnosis of peptic ulcer was made in four children. This would emphasize the importance of considering the possibility of occurrence of these inflammatory lesions in childhood. The rare reports of duodenitis in the pediatric literature suggest that both clinicians and roentgenologists may not be fully cognizant of the occurrence of these lesions in young patients. Undoubtedly some children with undiagnosed duodenitis have made an uneventful recovery with or without treatment. That a considerable number of these children with duodenitis develop chronic duodenal ulcer in adulthood is not certain. However, the studies on adults, the observations of Jankelson, and the coexistent chronic duodenitis and duodenal ulcer in one patient in this report indicate the possibility of such an occurrence.

Summary

Six cases of duodenitis in childhood are reported and the literature is briefly reviewed. Recovery was prompt and uneventful in all but one patient in this group. In the single instance chronic duodenitis existed for a period of four years despite a medical regime considered adequate. The possible presence of an inflammatory lesion of the duodenum should be considered in any child with vague or ulcer-like abdominal complaints. A clinical diagnosis can only be suspected and roentgen studies of the stomach and duodenum are indicated in cases of obscure gastric discomfort.

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Dr. Cesare Gianturco, Department of Radiology, Carle Memorial Hospital, Urbana, Ill., made the roentgenologic examination of all patients.

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SPANISH ABSTRACT

Duodenitis en la Ninez

Se reportan seis casos de duodenitis en niños, y conjuntamente se hace una revision de la literatura publicada. Del grupo de casos, todos se recobraron excepto uno, en el cual una duodenitis cronica existió por un periodo de cuatro años a pesar de un regimen considerado adequado.

La posibilidad de la presencia de una lesion inflammatoria duodenal debe ser considerada en niños con dolores abdominales vagos o de tipo ulceroso. El diagnostico clinico de duodenitis solo puedo sospecharse. Estudios radiologicos de estomago y duodeno están indicados en pacientes con dolores gastricos obscuros.

Carle Hospital Clinic

GLYCOGEN STORAGE DISEASE OF THE HEART

II. Critical Review of the Literature

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A CONSIDERABLE degree of confusion exists as to the true nature and definition of glycogen storage disease of the heart. Not all the abnormal conditions in which there is cardiac enlargement and an excessive deposition of glycogen in the fibers of the myocardium are instances of this disease. From a critical survey of the literature the authors have become convinced that the cardiac type of glycogen storage disease is a separate disease entity with distinctive clinical, pathologic and chemical manifestations and that definite criteria can be established after death for a case to be listed in this category. By following these specifications, true cases of this condition can be separated from other pathologic entities in which the finding of glycogen is a prominent feature.

The requirements to be fulfilled are of three orders: clinical, pathologic and chemical and can be listed as follows:

1. Marked enlargement of the heart.
2. Death within the first year of life.
3. Typical "lacework" appearance of histologic sections of myocardium, resulting from massive deposition of stored material in all cardiac fibers.
4. Chemical or histochemical demonstration of glycogen as the material causing infiltration of the myocardial fibers.

The criteria listed are concerned mainly with the heart, because the outstanding clinical and pathologic changes occur at this site, despite the fact that abundant glycogen storage is found in other tissues as well.

In a diligent survey of the literature only 12 cases have been found besides the two presented in a previous paper,[1] making a total of 14, that meet all the requirements listed and can therefore be considered true cases of glycogen storage disease of the heart.[1-18] There are several others which are clinically and pathologically typical, but in which recognition of glycogen by chemical or histochemical methods was not performed or not possible because of a previous fixation of the material in an aqueous solution of formalin.[4,19,20] Some of these cases were diagnosed pathologically as diffuse rhabdomyomas and others as cardiomegalia glycogenica diffusa. Such reports are not included in this survey even though it is recognized that they are very probably cases of glycogen storage disease of the heart.

I. CLINICAL FINDINGS

The most important clinical features in the 14 cases of glycogen storage disease of the heart reported in the literature are summarized in table 1. Unfortunately the reports are very incomplete; in some instances (Case 7) clinical details are almost entirely lacking. The impression given by the available data, however, is that of an illness which is remarkably constant in its manifestations and in its course.

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TABLE 1

Clinical Findings in Cases of Glycogen Storage Disease of the Heart

Case No.	Author	Sex	Color	Age at onset	Symptoms	Phys. exam. on adm.
1.	Sprague, Bland and White (1931)[2]	M	W	3 mo.	Failure to gain wt.; "quick" breathing; intermittent cyanosis	Malnutrition; macroglossia; enlargement of heart; apical systolic murmur.
2.	Pompe (1932)[3,4]	M	W	6¾ mo.	Fever and cough for 5 days	Marked cyanosis; patient acutely ill; bronchial breathing over left hemithorax; heart not "enlarged"; no murmurs; liver just palpable.
3.	Putschar, Bischoff (1932)[5,6]	M	W	Birth	Weakness; poor appetite; poor wt. gain; mental retardation.	Malnutrition; cyanosis; heart enlarged; liver palpable 4 cm. below costal margin.
4.	Antopol, Heilbrunn and Tuchman (1934)[7]	F	W	3½ mo.	Failure to gain wt. for 4 wk.; "unusually rapid" breathing since birth.	Fairly well nourished; acutely ill (no statement as to heart).
5.	Humphreys and Kato, Case I (1934)[8]	F	—	Birth	Always took feedings poorly and gained wt. slowly; fever and cough 4 days' duration.	Malnourished, dehydrated, weak, listless; labored breathing and cyanosis; heart enlarged, soft apical systolic murmur; liver and tip of spleen palpable.
6.	Humphreys and Kato, Case II (1934)[8]	F	—	2 mo.	Restless, poor appetite, lost wt.	Acutely ill with high fever; heart enlarged (no statement as to murmurs); liver enlarged.
7.	Van Creveld (1934)[9,10]	—	W	—	—	—
8.	Wolff (1936)[11]	—	W	Birth	Always took feedings poorly; was always sickly; 10 days' fever and cough; would take bottle only sitting up.	Malnutrition; macroglossia; cyanosis; "visible" enlargement of heart (no statement as to murmurs).
9.	Manca, Muggia (1936)[12,13]	F	W	20 days	Frequent projectile vomiting; "crises" of dyspnea and cyanosis.	Acutely ill, pale and cyanotic; heart enlarged; rough systolic murmur at base.
10.	Hertz, Jeckeln (1937)[14,15]	M	W	Birth	Poor feeding, frequent vomiting; listlessness; difficulty in breathing; attacks of cyanosis.	Small, poorly nourished, poor muscular tone; macroglossia; heart tones "clear"; liver 1 finger below C.M.; hypothermia.
11.	Mutgeert, Mansens (1937)[16,17]	F	W	Birth	Poor wt. gain and difficult feeding since birth; "rapid" breathing since 1 mo. of age; flaccid and drooping for few weeks.	Acutely ill; dyspnea and cyanosis; left hemithorax protuberant; heart enlarged; apical systolic murmur.
12.	Wachstein (1947)[18]	F	W	Birth	Poor feeding; failure to gain wt.; large loose, foul stools.	Malnourished, moribund; dyspnea and cyanosis (no statement as to heart).
13.	di Sant'Agnese, Andersen, Mason, Bauman (1950), Case I[1]	F	W	Few weeks	Poor development and wt. gain; "heavy" breathing; cyanosis.	Moribund; malnourished; macroglossia; pitting edema of hands and feet.
14.	di Sant'Agnese, Andersen, Mason, Bauman (1950), Case II[1]	M	W	Few weeks	Poor development and wt. gain; "heavy" breathing; intermittent cyanosis.	Malnourished; chronically ill; heart enlarged; soft apical systolic murmur; liver 3 cm. below C.M.; spleen tip palpable.

ECG	Roentgenographic exam.	Terminal episode	Time in hospital	Age at death	Family history
No axis deviation. P–R interval 0.06 sec. S–T segment: low take-off. *T wave:* Inverted in leads I and II, diphasic in lead III.	Left side of chest obscured by inflammation. Right border of heart "approx. normal."	Febrile illness; increasing cyanosis.	6 days	7 mo.	Father, mother and 1 sib normal. One sister died at 6 mo. of age after similar course: "quick" breathing, difficulty taking bottle; heart enlarged to percussion and globular by RG; soft systolic murmur.
———	———	Febrile illness; marked cyanosis.	3 days	7 mo.	———
———	Enormously enlarged (globular heart)	Febrile illness; increasing dyspnea and cyanosis.	21 days	4 mo.	Family history stated to be noncontributory. No siblings; mother had 1 miscarriage.
———	Marked total enlargement of heart.	Febrile illness; cyanosis; loss of wt.	10 days	5 mo.	———
———	Heart greatly enlarged. Left lung consolidated.	Increasing fever.	1 day	5 mo.	Normal healthy parents. No siblings.
———	Unusual cardiac enlargement.	Cyanosis	4 days	8 mo.	Twin brother well. No other details.
———	———	Bronchopneumonia	—	6 mo.	———
———	———	———	—	5 mo.	———
———	———	Sudden heart failure after crying.	Few hours	37 days	Only child ? healthy parents.
———	Heart enlarged in all diameters in ant.-post. projection.	Sudden collapse; erysipelas.	29 days	40 days	Only child (illegitimate). Father and mother well.
No. axis deviation. P–R interval 0.10 sec. P wave notched. *T wave:* neg. in I and II lead, pos. in III lead.	Confirm findings on physical examination.	Increasing dyspnea and cyanosis.	5 days	6½ mo.	Father and mother well. Brother died previous year at 6 mo. of age with symptoms similar to patient: heart enlarged to percussion; no murmur; large, globular heart by RG.
———	———	Heart failure.	Dead on Admission	10 wk.	Mother, father, 3 siblings, living and well. No consanguinity between parents.
———	———	Heart failure.	9 hr.	4 mo.	See case 14 (sibling).
Marked left axis deviation. P–R interval 0.08 sec. S–T segment depressed. *T wave:* Diphasic in lead I, inverted in leads II, III, IV.	Heart markedly enlarged in all diameters (globular heart)	Heart failure; bronchopneumonia.	33 days	4 mo.	Mother and father first cousins Parents and 6 siblings living and well. Sister died of same disease (case 13). Two other siblings died at same age and with similar symptoms.

There was no sex predilection, 6 of the reported cases were males, 6 were females, in 2 instances the sex was not given. Twelve patients were white. In the 2 reported by Humphreys and Kato (Cases 5 and 6) from this country, the race was not mentioned. All patients died before the eighth month of life: 11 between 4 and 8 months of age, 3 respectively at 37 days, 40 days and 10 weeks of age.

In six cases the onset of symptoms was noted at birth, in seven a few weeks to six months after birth, in Case 7 no age of onset was given. Poor feeding, listlessness and failure to gain weight properly seem to have been prominent among the early complaints. Intermittent cyanosis, especially during feeding, and attacks of dyspnea became the most distressing manifestations shortly after the onset of symptoms. Indeed, "excessively rapid breathing" was mentioned by several parents as the cause of their concern.

In seven cases the patients were either moribund or very acutely ill on admission and eight of them were in the hospital for less than a week, some only for a few hours before they died. Malnutrition was specifically described in nine cases, while in four others no mention was made of the nutritional status and in only one case (Case 4) was it stated that the child was "fairly well nourished." Macroglossia was noted in four cases (Cases 1, 8, 10, 13), and in one this feature was so pronounced as to lead to a clinical diagnosis of cretinism (Case 10). Cyanosis was recorded as being found on physical examination in six cases. In seven patients the area of cardiac dullness was found to be markedly enlarged on percussion, in six no details were given and in one case (Case 2) it was stated that the size of the heart on physical examination was thought to be normal. Of special interest is the finding of a heart murmur in four cases. In three this was a soft apical systolic murmur and in the fourth a rough systolic murmur best heard over the base of the heart. In three patients it was stated that no murmurs were present. In the other seven cases details as to the physical examination of the heart were missing. The liver was found to be palpable to moderately enlarged in four cases, but in no instance was the degree of enlargement very remarkable. The tip of the spleen was palpable in two patients. In several cases dullness, increased breath sounds and rales were found over the left hemithorax.

The terminal episode in all cases was heart failure, complicated in seven instances by an acute febrile illness, usually a bronchopneumonia. In some patients cyanosis and dyspnea had been present for some time, but the end was usually fairly sudden and dramatic.

Roentgenologic findings were much more consistent than the physical findings. In seven out of the eight cases in which a roentgen examination of the chest was performed the heart was found to be markedly enlarged. The increase was equal in all diameters and the heart shadow was generally reported as being "globular." In the eighth patient (Case 1) it was reported that "the right cardiac border appeared to be normal," but that the rest of the heart could not be seen because the whole left side of the chest was obscured by the presence of fluid. In two other cases consolidation of the left lung was reported.

Electrocardiographic findings: Electrocardiograms were obtained in Cases 1, 11 and 14. Sprague, Bland and White did not describe the ECG in their original report,[2] because they thought the low take-off of the S-T segment was due to artefact. This tracing was published in 1940 by Schnitker.[21]

In Case 14 there was marked left axis deviation; in the other two cases no axis deviation was present. The absence of right axis deviation in infants of this age is in itself pathologic and equivalent to left axis deviation in an older age group. The T waves were inverted in two out of three leads in Cases 1 and 11, in three out of four leads in Case 14. The S-T segment was depressed in Cases 1 and 14. The P-R interval was normal in all instances.

The QRS complex was not prolonged or deformed in any of the cases.

Inverted T waves and low voltage curves in the ECGs of infants with hypertrophied hearts have been considered diagnostic of anomalous origin of the left coronary artery.[22,23] However low voltage waves are not always present in such cases[24] even though T waves are inverted. It has also been seen that inversion of the T waves, though without the accompanying low voltage, occurs in glycogen storage disease of the heart. Whether in these latter cases the changes were due to myocardial damage or to the presence of marked left axis deviation is not clear. It is probable that inversion of the T waves occurs in other conditions characterized clinically by hypertrophy of the heart in infancy. It was seen recently at Babies Hospital in a case later proved at autopsy to have subendocardial fibro-elastosis. It does not seem possible, therefore, to make a differential diagnosis between conditions characterized by hypertrophy of the heart in infancy on the basis of the electrocardiographic findings.

Family History: The family history of Cases 13 and 14 has been reported in detail in a previous paper.[1] These two patients were siblings and their parents first cousins. There are two other instances in the literature (Cases 1 and 11) in which the family history suggests that a sibling of the patient reported died in infancy of a similar condition. In neither of these cases was there any known consanguinity between parents. In four instances the patient described was the only child and in four others no details were given as to the family history.

II. Pathologic Findings

Macro- and microscopic findings at postmortem examination were so similar in all instances that a summary description can be given to apply to all cases.

The outstanding findings on gross examination were in the heart, which in all cases was enormously enlarged, weighing from 2 to 5.6 times the normal for the age. The shape of the heart was also distinctive, being of a round, globular appearance with great hypertrophy and dilatation of the ventricles, but with no increase in size of the auricles. On section, enormous thickening could be seen of the wall of the left ventricle, of the interventricular septum and to a lesser extent of the right ventricle. In contrast the walls of the auricles were not increased in thickness. The color was also unusual, being a pale pink and quite different from the usual color of the myocardium. No other defects of significance in the heart were noted, in particular in no case was there any abnormality of the coronary arteries.

Histologically the massive infiltration of the cardiac fibers by glycogen leads to a distinctive microscopic picture with a "lacework" appearance of the myocardium. Each fiber was like a hollow cylinder surrounded by thin delicate cytoplasm, the nucleus lying free in the center. At times the change in structure was so great as to make recognition of the myocardial tissue difficult. The single myocardial fibers were frequently enlarged, as in Case 14, but in Case 9 they were smaller than normal. Whether this difference in size was due to difference in age cannot be established, because details as to size of the fibers were missing in most cases.

Striking changes were found in the skeletal muscles in six cases (Cases 2, 5, 7, 8, 10, 14). Mild vacuolization of striate muscle fibers was described in two of the younger infants, Case 9, aged 37 days, and Case 12, aged 10 weeks. Best's carmine stain has been used to identify glycogen in all these cases. These changes in striate muscle were first remarked upon by Humphreys and Kato[8] in 1934, who gave an excellent description of them. The average diameter of the fibers is increased from 2 to 5 times the normal. The increase is

due to the vacuolization, which varies in degree. Moderately affected fibers have rows of vacuoles lying between fibrillae, while in the larger fibers the entire cytoplasm appears replaced by glycogen. The amount of glycogen present varies greatly in different muscles; the tongue is consistently and severely affected, the diaphragm much less so, while the muscles of the neck, extremities and trunk have a variable degree of excess. It is interesting that the histologic changes and the increased glycogen content by chemical determination were present in the tongue irrespective of whether macroglossia was noted clinically or not.

The smooth muscle also contains an excess of glycogen in many instances. The media of small and large arteries has been most often remarked on, but glycogen has also been demonstrated in the smooth muscle fibers of the bronchial mucosa (Case 14), esophagus (Cases 8 and 14), intestines (Cases 9, 12 and 14, but not Cases 5 and 8), renal pelvis (Case 14), bladder and ductus deferens (Case 5).

The cells of the reticulo-endothelial system, including the vascular endothelium, reticulum cells of the spleen, lymph nodes, bone marrow and thymus and the Kupffer cells, have been found to contain glycogen in one or more cases. In one instance, the glycogen content of the Kupffer cells was scanty (Case 10).

The weight of the liver was recorded in Cases 3, 5, 10 and 14. The weights varied from 11% to 60% above the normal for the age. The liver was said to be enlarged in five other cases and normal in one. The histologic changes in the parenchymal cells were striking; large amounts of glycogen were found in vacuoles within the hepatic cells.

The weight of the kidneys was recorded in these same cases and varied from 16% below normal to 20% above the normal for the age. The kidneys were said to have appeared normal in size in five other cases. Glycogen has been found regularly in the epithelium of Henle's loop, the collecting tubules and the pelvic epithelium, but the convoluted tubules and glomeruli are affected in some cases and not in others.

Other epithelial cells which have been described as showing an excess of glycogen with Best's stain are the mucous glands, but not the other glands, of the gastrointestinal tract; the acini, ducts and islet cells of the pancreas; and the cortical and medullary cells of the adrenal. It has also been described in hair follicles.

There is therefore evidence of abnormal glycogen deposition in a variety of cell types throughout the body. Although the symptoms have been attributed to the myocardial lesion, it is possible that they may in part be due to dysfunction of arterial muscle, striate muscle and the parenchymal cells of viscera which are affected.

III. Chemical Studies

1. Clinical laboratory studies: Most patients died a few hours or days after admission to the hospital and before the diagnosis was suspected, so that few clinical studies were performed. Clinical laboratory studies are reported in only 6 of the 14 cases. Urine analyses were performed in all these patients and revealed the absence of acetone and, in the two instances in which it was looked for, of diacetic acid. A total of 17 determinations of fasting blood sugar were done in three patients and all failed to reveal blood sugar levels within the hypoglycemic range, although the values were at times in the lower range of normal. It should also be noted that in no instance were hypoglycemic symptoms reported. Oral glucose tolerance tests were carried out in three cases, a flat curve being observed in two patients. In the third patient (Case 11), the rise of blood sugar after ingestion of glucose was within normal limits, but the curve was diphasic. The significance of this finding was not interpreted. The only intravenous dextrose tolerance test carried out gave a normal

curve. Galactose tolerance tests were performed in two cases; and while the results were within normal limits in Case 14, the curve of total blood sugar was abnormally high in Case 11. This is the same patient who had a diphasic oral glucose tolerance curve. It should be noted, however, that while the dose of galactose administered to this infant was quite comparable to the one given to Patient 14, no provision was made in the blood sugar determinations to differentiate between glucose and galactose. The figures given represent only total blood sugar, and it is impossible to tell whether the abnormally high total sugar curve in the blood was due to poor handling of galactose or to an abnormally great liberation of dextrose by the liver after galactose ingestion. An oral levulose tolerance test done in Case 14 was found to be normal.

The glycemic response to subcutaneous injection of epinephrine was investigated four times in three patients and found to be normal in all cases. This is a finding of great theoretic interest, because it shows the mechanism of glycogen accumulation to be entirely different from that of glycogen storage disease of the liver (Von Gierke's disease) in which injection of epinephrine characteristically elicits no increase in blood sugar.[25,26] The blood lactate response to injection of adrenaline was determined in Case 14; its significance has been discussed in a previous paper.[1]

The glycogen level in the blood was determined in two cases and considered in both instances to be within normal limits. It should be noted, however, that in van Creveld's patient (Case 7) the determination was performed after death, while in the patient of Mutgeert and Mansens (Case 11) the values were considerably higher than those usually regarded as normal.[9] The fact that the latter authors determined the blood glycogen level in two normal children and obtained figures comparable to those found in their patient leads one to wonder whether the method which they used was responsible for the high readings recorded.

Fat metabolism was investigated in two patients, and in both instances all values obtained were within normal limits. Numerous other chemical tests were done in Case 14 and. as pointed out previously, all gave normal values.

In conclusion, in the five cases in which clinical chemical determinations were performed no abnormalities were found except oral dextrose and galactose tests in Case 11, both of which are of uncertain interpretation.

2. Postmortem chemical studies: Postmortem chemical determinations of glycogen were performed in six cases. The results of these analyses are detailed in table 2. All figures given express the glycogen content in relation to wet weight of the organs analyzed, with the exception of Case 8 for which only the figures for dry weight were available. In Case 4 chemical analysis was performed only after the organs had been kept for two weeks in an aqueous solution of formalin, so that undoubtedly part of the glycogen had passed into solution in the fixative.

The results of the chemical determinations in Cases 7, 10, 11 and 14 are directly comparable and remarkably uniform. It is stated by Bridge and Holt[26] that a glycogen content of 15% of the wet weight is probably a maximal figure for the human liver in hepatic glycogen storage disease. In all probability 10% is as much as can be stored by the human heart before the accumulation becomes incompatible with cardiac function.

It should be noted that the glycogen content of striate muscle and of the tongue in the cases in which it was determined was very similar to that of the heart, confirming the impression that the abnormal accumulation of glycogen was not limited to the latter organ.

The glycogen content of the liver was also similar to that of the heart in all cases.

Hepatomegaly was never very great, however, so that the total amount of polysaccharide present in the liver was much smaller than in cases of the hepatic type of glycogen storage disease.

Great variation was found in the glycogen content of the kidneys. In no instance were the kidneys greatly enlarged.

TABLE 2

POSTMORTEM CHEMICAL DETERMINATIONS OF GLYCOGEN IN CASES OF GLYCOGEN STORAGE DISEASE OF THE HEART

Case No.	Time after death autopsy performed	Per cent glycogen content (Dry weight in Case 8, wet weight in all others)						Auto-glycogenolysis
		Heart	Skeletal muscle	Tongue	Liver	Kidney	Other organs	
4*	Not given	3.57	—	—	3.25	4.34	Lungs 0.32	—
7	Not given	7.97	9.39	—	9.13	—	Spleen 1.46 Adrenal 1.25 Lung 0.034 Spinal Marrow 0.583	In liver: Not done In heart: 15% } In 48 hr. at 37°C.
8	Not given	33.20	—	35.30	11.70	6.95	—	—
10	17 hr.	7.90	5.47	3.58	4.12	1.22	—	In liver: Complete In heart: 50% } In 24 hr. at 37°C. in buffer solution
11	Several hours	10.00	—	—	6.00	—	—	—
14	90 min.	9.80	6.28	6.61	7.12	0.39	—	In liver: Complete In heart: 83% } In 24 hr. at 37.5°C.
Normal values (9)	—	0.07	0.011	—	0.103	0.062	Spleen 0.01	—

* Kept in aqueous solution of formalin for 2 wk. before chemical determination.

Of great interest are the experiments of auto-glycogenolysis performed in three cases (table 2). In Case 7 there was a decrease of only 15% in the glycogen concentration in heart tissue after incubation for 48 hours at 37° C. Unfortunately no details are given as to methods followed or time after death when the material was collected for examination.

In Case 10 minced tissues of the liver and heart were suspended in a buffer solution of pH 6.5-6.9 and incubated at 37° C. In Case 14 minced tissues of the various organs were incubated at 37.5° C. without the addition of buffer.

In Case 14, 97% of glycogen disappeared from the liver in 24 hours. In Case 10 the liver glycogen content decreased by 37% in 24 hours and by 97% in 48 hours. The decrease in glycogen content of the heart was 83% for Case 14 in 24 hours, about 50% in 26 hours in Case 10. No later determinations were made in Case 14, but the polysaccharide content of the heart had not further diminished in Case 10 four days later.

Spontaneous glycogenolysis therefore took place in both Cases 10 and 14. It is possible that the difference in the rate and extent of glycogen disappearance between the two cases may be explained by the use of a buffer solution in Case 10, which may have interfered somewhat with glycogenolysis. By and large, however, the similarity of the

findings in Cases 10 and 14 is noteworthy, leaving the discordant results of Case 7 without satisfactory explanation.

Experiments of auto-glycogenolysis were performed in other organs only in Case 14. The results have been presented elsewhere.[1]

Discussion

1. *Glycogen storage disease of the heart:* It is obvious from what has been said that glycogen storage disease of the heart is a separate entity with distinctive clinical, pathologic and chemical manifestations. Because of the uniformity of the findings in all reported cases it is possible to establish definite criteria for the recognition of true cases of this disease. These have been listed previously in this paper.

Glycogen storage disease of the heart is a rare condition. Only 14 proved cases were found in a careful search of the literature and only two cases, both in the same family, have been seen at the Babies Hospital in New York in 27 years and out of 2000 autopsies. A disease of early infancy resulting in death a few weeks or months after birth, it is characterized clinically by signs of heart failure and by an enormous enlargement of the heart, which is found even more consistently on roentgen than on physical examination. So far as can be judged from the meager genetic information available the condition may be provisionally classed as a hereditary error of metabolism, transmitted by a recessive gene. It is impossible from the data on hand to be sure where the defect lies. The suggestion has been offered[1] that the abnormality might consist in the formation of a polysaccharide closely allied to glycogen, but differing from it in its structure thus disturbing the chemical equilibrium in favor of an accumulation of polysaccharide. Another explanation offered[1] is that these individuals are unable to convert the excess carbohydrate absorbed to fat as ordinary individuals do, with resulting excessive deposition of glycogen. Both these suggestions are of course still in the nature of hypotheses.

It should be pointed out that the chemical and histochemical methods employed by the majority of the investigators are by no means specific[27] and cannot differentiate between glycogen and closely allied polysaccharides. However, there is no other condition known which gives a polysaccharide infiltration of similar magnitude and with such distinctive pathologic changes.

Ample evidence exists to show that the accumulation of glycogen involves not only the heart, but the striate muscle, the smooth muscle and probably other organs and tissues. It is not possible with the information at hand to determine whether all these are equally affected in all cases. The reactions of extrahepatic carbohydrate metabolism are more or less uniform throughout all parts of the body; and if a defect exists at some point in the cycle causing accumulation of glycogen, this would be expected to be found in all tissues. Such may indeed be the case, but figures are not available for comparison of normal and abnormal glycogen content except in the heart, skeletal muscle, liver and kidneys.

Whatever the mechanism, glycogen storage disease of the heart is incompatible with life for more than a few months, during which cardiac function continuously regresses. The most plausible explanation is that of mechanical death produced by an accumulation of glycogen in the myocardial fibers to a point where their contraction is impeded and effective cardiac action no longer possible.

Because of the existence of abnormal glycogen accumulation in other parts of the body the term "glycogen storage disease of the heart" is obviously a misnomer. On the other hand, the outstanding clinical and pathologic manifestations are to be found in this site;

furthermore tradition has sanctioned the use of this name. It is suggested therefore that it be retained. The synonyms "cardiac type of glycogen storage disease" and "cardiomegalia glycogenica diffusa" are descriptive appellations that can also be used. A strong plea is made, however, for dropping the name "Von Gierke's disease of the heart." This term leads to confusion with the hepatic type of glycogen storage disease, an entirely different pathologic entity. "Pompe's disease of the heart" might be substituted with greater accuracy.

2. *Relation of the cardiac to the hepatic type of glycogen storage disease:* Mason and Andersen in 1941[25] pointed out the wide variation in the metabolic findings described in cases cited as examples of glycogen storage disease of the liver, and proposed that the term be limited to patients with hepatomegaly and failure of the glycemic response to subcutaneous injection of epinephrine. Bridge and Holt[26] stressed again the belief that the hepatic type of glycogen storage disease constituted a separate clinical and physiologic entity and listed the criteria that should be met to establish the diagnosis. These included: marked enlargement of the liver, rapid development of hypoglycemia and ketosis when food is withheld, subnormal or absent glycemic response to injection of epinephrine, abnormal stability of the liver glycogen after death, chemical analysis showing a markedly increased hepatic glycogen content. Table 3 shows that except for the last none of these conditions is met in the cardiac type of glycogen storage disease.

It has long been recognized that the hepatic and the cardiac types of glycogen storage disease differ in their clinical manifestations. The comparison in table 3 shows that we are dealing with two distinct diseases, with an entirely different metabolic background. In the hepatic type of glycogen storage disease the defect lies in the inability of the liver to convert glycogen to glucose and probably glucose to glycogen.[25,26,28] Glucose is not available to the tissues, which therefore burn fats in large amounts. The hypoglycemia and the ketosis so characteristic of the disease are the consequence. This sequence of events does not take place in the cardiac type of glycogen storage disease.

Yet despite the differences there undoubtedly are similarities, e.g., the glycogen accumulation, which does not occur in the same form and to the same extent in any other disease, and the familial incidence, which was present in two cases of the cardiac type (Cases 13 and 14) and very probably in two others (Cases 1 and 11) and has been noted several times in the hepatic type.[28] Consanguinity in the parents has been mentioned by three authors[4,29,30] in cases of the hepatic type of glycogen storage disease, and was also present in the two cases (Cases 13 and 14) of the cardiac type reported in this paper. This certainly suggests that both conditions are hereditary and recessive in character. There is no instance on record, however, in which the cardiac and hepatic types of the disease have occurred in the same family. This is further evidence that the metabolic error is entirely different in the two conditions.

3. *Other conditions in which excess of glycogen is present in the myocardium:* There are in the literature a number of reports of cases not meeting the requirements previously outlined for glycogen storage disease of the heart, but in which abnormal deposition of glycogen in the myocardium has been shown histochemically after death. In many of these patients marked enlargement of the heart was present both clinically and pathologically.

These cases can be divided into four groups: rhabdomyomas of the heart, cardiomegalia glycogenica circumscripta, cases of sudden death in which postmortem examination has shown a large heart and a diffuse, but not massive, deposition of glycogen in the cardiac

muscle and other organs, and finally unclassified cases. In the first two groups the abnormal glycogen accumulation was focal and limited to certain areas of the myocardium.

a. Rhabdomyomas and rhabdomyomatosis of the heart: Rhabdomyomas or congenital glycogenic tumors of the heart were described for the first time in 1862 by von Recklinghausen. Since then many cases have been described and in 1945 Batchelor and Maun[31]

TABLE 3

CLINICAL AND METABOLIC DIFFERENCES BETWEEN HEPATIC AND CARDIAC TYPES OF GLYCOGEN STORAGE DISEASE

		Hepatic type	Cardiac type
Clinical Data	Onset	Early infancy to after 1 yr. of age	Birth to 1–2 mo. of age
	Physical findings	Marked enlargement of liver Physical retardation	Marked enlargement of heart. Cyanosis, dyspnea
	State of nutrition	Nutrition fair, occasional obesity	Malnutrition, marked
	Symptoms of hypoglycemia	Frequently present	Absent
	Course	Life for several years	Death between 1 mo. and 8 mo. of age
	Mode of death	Intercurrent infection or acidosis	Heart failure
Carbohydrate Metabolism	Extent of glycogen deposition	Liver, sometimes kidneys	Heart, striate and smooth muscle, liver and most other organs
	Hypoglycemia	Present	Absent
	Resting blood lactate	Frequently elevated	Normal
	Glycemic response to epinephrine	None	Normal
	Lactic acid response to epinephrine	None	Normal
	Dextrose tolerance curve	High rise	Normal
	Galactose and levulose tolerance curves	Flat or normal	Normal
	Blood glycogen	Increased	Normal
	Insulin tolerance test	Impaired	—
	Postmortem auto-glyco-genolysis Liver	None	Normal
	Postmortem auto-glyco-genolysis Heart	—	Present, probably normal
Fat Metabolism	Serum lipids	Frequently increased	Normal
	Serum cholesterol	Frequently increased	Normal or low
	Ketonuria after fasting	Marked	Absent

were able to find 63 cases in the literature. Rhabdomyomas are usually multiple, but a few examples of single tumors of the myocardium have been reported.[32,33] In three cases a diagnosis of diffuse rhabdomyomatosis of the myocardium was made,[31] but it is now recognized that these in all probability were cases of glycogen storage disease of the heart, the existence of which was not generally known at the time when these reports were published. In the great majority of cases multiple rhabdomyomas of the heart have been associated with tuberous sclerosis of the brain.

Clinically rhabdomyomas may or may not cause symptoms and have been noted in patients at various ages including adults. More than half the cases reported have been in infants under 1 year of age.[31] In infancy the condition does not usually give rise to enlargement of the heart.

Typically rhabdomyomas consist of multiple nodules scattered through the ventricular and auricular myocardium, as can be seen in a photograph of the gross specimen in the paper by Olsen and Cooper.[34] Microscopically the nodules consist of large vacuolated muscle cells containing large amounts of glycogen. At times these cells assume a characteristic appearance described by the term "spider cell," first applied by Cesaris-Demel.[35]

There has been some discussion[34,36] as to whether the nodules represent true neoplastic tissue or a developmental disturbance with secondary degenerative changes. Because of the latter view the term rhabdomyomatosis of the myocardium has been preferred by some authors.

A few investigators have interpreted some of the cases of rhabdomyomatosis as transitional or localized form of glycogen storage disease of the heart.[34,37,38] The present investigators cannot agree with this view.

b. Cardiomegalia glycogenica circumscripta: This term was coined by Finkelstein[39] in 1936 to describe a case of cardiac enlargement in which he was able to demonstrate areas containing glycogen. The patient, a 10 month old infant, had been reported in 1924 by Carrington and Krumbhaar, who had described an anomalous origin of the left coronary artery from the pulmonary artery, which at the time was not felt to be sufficient to explain all the changes in the heart. When the cardiac type of glycogen storage disease was described by Pompe and others around 1932,[3-6] Finkelstein stained sections from the original paraffin blocks and found localized accumulations of glycogen in degenerated cells scattered in groups of irregular form in the myocardium. A considerable degree of fibrosis and round cell infiltration was also present. Because of the presence of glycogen he thought that in this case there was an anomaly of metabolism similar to that of glycogen storage disease of the heart resulting in a localized accumulation of the polysaccharide. It is now recognized, however, that anomalous origin of the coronary arteries is one of the causes of enlargement of the heart in infancy.[23] Histologic changes such as those described by Finkelstein may be found in such cases in the portions of the myocardium supplied by the anomalous vessels.

The same term was applied by van Creveld and van der Linde[40] in 1939 to describe the case of a 5 month old infant with a large heart in whom after death areas of glycogen accumulation were found in the myocardium. There was no anomaly of the coronary arteries in this case, but the foramen ovale and the pulmonary artery were abnormally large. As in Finkelstein's case the degenerated cells containing glycogen were irregularly distributed throughout the myocardium. Areas of necrosis, fibrosis and of cellular infiltration were also present. Chemical determination of glycogen concentration in the myocardium revealed it to be 0.5%.

In this general category must also be placed the case of a 15 year old boy reported by Antopol and collaborators in 1940.[41] Here again, the heart was markedly enlarged, glycogen was deposited in irregular areas throughout the myocardium, fibrosis and round cell infiltration were prominent features. Coronary arteries were normal. The chemical analysis in this case revealed a glycogen content of the heart of 4%.

It is seen that the term cardiomegalia glycogenica circumscripta was based on two

erroneous assumptions: that anomalous origin of the coronary artery could not explain the clinical picture and pathologic findings, and that the presence of glycogen in the myocardium implies glycogen storage disease. Van Creveld's and Antopol's cases were quite different in etiology, although showing similar pathologic changes. It seems probable therefore that cardiomegalia glycogenica circumscripta does not exist as a disease entity.

It has been observed by the present authors and others[42] that areas of degeneration, fibrosis and round cell infiltration of the myocardium occur in cases of anomalous origin of the coronary artery. The degenerated areas are irregularly scattered through the myocardium, poorly circumscribed and sometimes wedge-shaped, an appearance which is quite different from the round, nodular accumulations seen in rhabdomyomata. The fibers themselves are large, vacuolated, with a nucleus compressed at the periphery and in no way distinguishable, cell by cell, from those found in other conditions in which there is glycogen accumulation in the myocardium.

It seems probable, therefore, that in myocardial fibers which have degenerated as a consequence of circulatory disturbance glycogen can be demonstrated as the substance which fills these vacuolated fibers. Since the description of glycogen storage disease of the heart, pathologists have been aware of this possibility and have occasionally stained the sections for glycogen with positive results. It must be stressed that the mere presence of glycogen in the myocardium does not provide a basis for a diagnosis of glycogen storage disease since glycogen is a normal component of myocardial cells and can be increased under various pathologic conditions.

c. Cases of sudden death with glycogen in the myocardium: The presence of glycogen in the myocardium has been described in cases of sudden death in childhood.

Giampalmo[43] reported on four infants who died suddenly, a diagnosis of "thymic" death being made clinically. In all four patients some glycogen was found in the cardiac muscle but the infiltration was especially marked in the first case described. Even in this patient, however, the glycogen deposition was not uniform throughout the myocardium.

Schneider[44] in 1945 described the case of an infant 9 months of age who died suddenly after being apparently well. Although the appearance of the heart muscle was not grossly altered, edema and glycogen deposition in the myocardial fibers was found. The liver and spleen were markedly enlarged. This same case was also briefly reported by Scheidegger[45] in 1945.

Case I of Gardner and Simpson[46] was an 11 year old boy in apparent good health who died suddenly and in whom at autopsy an enlargement of the heart was found. Large amounts of glycogen were demonstrated histochemically in the cardiac fibers. Unfortunately only one photomicrograph is given and the reproduction is not clear. If the criteria previously outlined are correct, because of the age of the patient, the absence of the typical clinical picture and the lack of other details this case cannot be accepted as one of glycogen storage disease of the heart.

It is not possible to determine whether the patients described by Giampalmo and by Schneider died of the same illness. The significance of the presence of glycogen in the myocardial fibers was also not clear. Whether it is increased in amount in all patients who have died a sudden death is not known.

d. Unclassified cases: In 1944 Bonaba and collaborators[47] reported the case of an infant who was ill from the age of 1 month and died when 3½ months of age. A roentgenographic examination had shown the heart to be enormously enlarged. At autopsy

an equal hypertrophy of both auricles and ventricles was present. Microscopically the cardiac fibers were found to contain numerous granules identified histochemically as glycogen.

This case may be one of glycogen storage disease of the heart, but because of the lack of details it cannot be definitely accepted as such.

4. *Relation of glycogen storage disease of the heart to so-called "idiopathic cardiac hypertrophy" in infancy:* The existence of a large group of obscure cases of cardiac enlargement and cardiac failure in infancy has long been recognized.[23] When glycogen storage disease of the heart was described by Pompe in 1932, it was thought that an explanation for these cases had been found. It became clear subsequently that not all cases of idiopathic hypertrophy of the heart could be explained on this basis. Through the years a number of separate conditions have been described, all of which lead to cardiac enlargement in infancy. Among these can be mentioned: aberrant origin of the left coronary artery, acute interstitial myocarditis (Fiedler's myocarditis), subendocardial fibroelastosis, essential hypertension, transposition of the great vessels and others.

Judging from the literature and the experience at the Babies Hospital (p. 615), glycogen storage disease of the heart is one of the rarer causes of cardiac enlargement and heart failure in infancy.

5. *Differential diagnosis:* The possibility of glycogen storage disease of the heart should be considered whenever an infant's heart is found markedly enlarged in all diameters. There are no pathognomonic signs, no laboratory investigations which point to the right diagnosis. The finding of electrocardiographic changes does not differentiate between anomalous origin of the left coronary artery and glycogen storage disease of the heart; the absence of abnormalities in the ECG, however, militates against either condition.

The only finding which may point to the correct diagnosis is the histochemical demonstration of excessive deposition of glycogen on biopsy of skeletal muscle. The majority of cases reported to date have shown abnormal amounts of glycogen and the presence of a fairly characteristic type of degeneration of the striate muscle fibers.

More frequent performance of ante- and postmortem investigations in cases of glycogen storage disease of the heart will lead to a better knowledge of the pathogenic mechanisms operating in these cases. If further information is to be obtained, the disease must be suspected and the clinical investigations carried out promptly. Histochemical studies of a muscle biopsy may establish the diagnosis in vivo and permit clinical investigation of carbohydrate metabolism in known cases. For histologic demonstration of glycogen it is essential that the tissue be fixed in absolute alcohol, since most of the glycogen will otherwise be dissolved in aqueous fixatives. Studies of autoglycogenolysis in the liver, heart, tongue and skeletal muscle should also be carried out. It will be important to extract some of the glycogen stored in the heart and other organs of such a case and have it analyzed to determine its chemical structure.

Summary

Glycogen storage disease of the heart is a separate disease entity with distinctive manifestations. Clinical, chemical and pathologic criteria for diagnosis are listed.

In a survey of the literature 14 cases were found that fulfilled all requirements. The impression given by the available clinical data is that of an illness remarkably constant in its course and manifestations. Eleven of the 14 patients died between the ages of 4 and 8 months, and the other three at an earlier age. The electrocardiographic findings in three cases are discussed.

The pathologic changes were similar in all cases. The outstanding lesions were in the myocardium, but abnormal deposition of glycogen was not limited to this site, being found in many other organs and tissues. In 6 out of 8 cases in which histologic and histochemical studies of skeletal muscles were made, a distinctive type of degeneration was found together with an abnormally great accumulation of glycogen.

Analyses of blood and urine performed while the patients were still living were essentially normal. Postmortem chemical studies in six cases confirmed the morphologic demonstration of widespread distribution of glycogen throughout the body. Spontaneous glycogenolysis was shown to occur in the myocardium after incubation at 37° C. for 24 to 48 hours, although to a different degree in the three cases in which it was done. In two of these there was virtually complete disappearance of glycogen from the liver after incubation at 37° C. for 24 to 48 hours.

The cause of this rare disease is presumably an inborn error of metabolism transmitted as a recessive genetic character. Whatever the mechanism the condition is incompatible with life for more than a few months, during which cardiac function continually regresses. The most plausible explanation is that the accumulation of glycogen in the myocardial fibers progresses to a point where their contraction is impaired and effective cardiac action is no longer possible.

It is pointed out that the term "glycogen storage disease of the heart" is a misnomer, since the disease process is not limited to this organ. On the other hand, as tradition has sanctioned its use, the name may well be retained. A plea is entered for dropping the name "von Gierke's disease of the heart" as leading to confusion with other types of glycogen storage disease.

The clinical and metabolic differences between the hepatic and cardiac types of glycogen storage disease are detailed. Other conditions characterized by abnormally great accumulation of glycogen in the myocardium, such as congenital rhabdomyoma of the heart, so-called cardiomegalia glycogenica circumscripta, and occasional cases in which death is sudden though not always explained, are described and the differences with glycogen storage disease of the heart mentioned. Differential diagnosis is discussed and it is pointed out there are no pathognomonic signs or laboratory investigations, except for the histochemical demonstration of abnormal amounts of glycogen in the skeletal muscles. It is suggested that biopsy of skeletal muscle be performed in all cases in which unexplained enlargement of the heart in infancy occurs. This is essential in order to plan ante- and postmortem pathologic and chemical studies.

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Additional Note

Since this paper was submitted for publication, a fifteenth well documented case of glycogen storage disease of the heart was reported by D. H. Clement and G. C. Goodman in the *Journal of Pediatrics,* vol. 36, p. 11, 1950.

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SPANISH ABSTRACT

Enfermedad de Almacenamiento de Glucogeno del Corazon
II. Revision Critica de la Literatura

La enfermedad de almacenamiento de glucogeno del corazon es una entidad clinica separada con manifestaciones distintivas. Los autores describen los criterios clinicos, quimicos y anatomopatologicos necesarios para el diagnostico.

En una revision de la literatura medica, se encontraron 14 casos que llenaban todos los requerimientos diagnosticos. La impresion dada por los datos clinicos acumulados, es que esta enfermedad es extraordinariamente constante en su curso y manifestaciones. Once de catorce pacientes fallecieron entre los 4 6 8 meses de edad, y los otros tres pacientes fallecieron a una edad mas temprana. Las alteraciones electrocardiograficas ocurridad en tres casos son discutidas.

Los cambios patologicos fueron similares en todos los casos. Las lesiones principales se encontraron en el miocardio, pero una deposicion anormal de glucogeno fué además observada en muchos otros organos y tejidos. En seis de ocho casos en los cuales estudios histologicos y histioquimicos de los musculos voluntarios fueron hechos, se demonstró un tipo distintivo de degeneracion asociada con una gran acumulacion de glucogeno.

Analisis de sangre y orina realizados durante la vida de estos pacientes, fueron esencialmente normales. Estudios quimicos post-morten en seis casos, confirmaron la distribucion generalizada del glucogeno a traves del cuerpo. Glucogenolisis espontanea de diferentes grados, ocurrió en el miocardio incubado a 37 grados Centigrados por 24 a 48 horas. En dos de tres casos estudiados se demonstró una desaparicion completa del glucogeno del higado incubado a 37 grados Centigrados por 24 a 48 horas.

Se presume, la causa de esta enfermedad sea debida a un error congenito del metabolismo (inborn error), el cual es transmitido como un caracter genetico recesivo. Esta afeccion es incompatible con la vida por mas de unos meses, durante los cuales la funcion cardiaca se deteriora continuamente. La explicacion mas plausible, es que la acumulacion progresiva de glucogeno en las fibras del miocardio llega a un limite, en el cual las contracciones se deterioran y la funcion cardiaca efectiva es afectada grandemente. Se señala que el nombre de "enfermedad de almacenamiento de glucogeno del corazon" no es adecuado, ya que la enfermedad no se limita al corazon. Sin embargo, la tradicion ha sancionado

su uso y por lo tanto el nombre debe retenerse. Los autores sugieren que el nombre de "enfermedad de von Gierke del corazon" debe abolirse, para evitar la confusion con otros tipos de enfermedades de almacenamiento de glucogeno.

Se presentan las diferencias clinicas y metabolicas entre la formas hepatica y cardiaca de esta afeccion.

Se describen y se notan las diferencias, entre otras condiciones tambien caracterizadas por una gran acumulacion de glucogeno del miocardio, entre ellas; los rhabdomyoma congenitos del corazón; casos de cardiomegalia glycogenica circumscripta, y ciertos casos de muertes repentinas, a veces inexplicables. El diagnostico diferencial es discutido y se señala que no hay signos patognomonicos clinicos o de laboratorios a excepción de la demostración histioquimica de cantidades anormales de glucogeno en los musculos voluntarios. Los autores surgieren la obtencion de una biopsia de los musculos voluntarios, en niños con un aumento del tamaño del corazon de origen obscuro. Se indica que este examen es esencial, ya que sirve para planear los estudios quimicos y anatomo-patologicos ante-morten y post-morten.

Babies Hospital, 3975 Broadway

ANESTHETIC MANAGEMENT OF INFANTS AND CHILDREN DURING ENDOSCOPY

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ANESTHESIOLOGISTS have run the gamut of agents and technics in an effort to find an anesthetic procedure for endoscopy in infants and children which would be satisfactory to the surgeon and provide an adequate margin of safety for patients.

It has been advocated that bronchoscopy should be done in children without anesthesia.[1-3] Several definite objections may be raised: (a) The psychic trauma and physical pain accompanying bronchoscopy in the unanesthetized child may be frightening and make serial examinations in the same patient difficult or even impossible; (b) excessive activity on the part of the patient precludes accurate, careful study of the bronchi through a small bronchoscope; (c) the likelihood of trauma to delicate tissues is greatly increased and (d) the practice is unworthy of modern medical science.

Ethyl ether by the open technic has been employed with varying degrees of success. In spite of the presumed wide margin of safety with this method the disadvantages are many. Placing a mask over the child's face is usually enough to make future induction of anesthesia distasteful to everyone concerned. With ether the child must be deeply anesthetized. The anesthesiologist is then required to step away from the patient while the examiner proceeds with endoscopy. The operator is subjected to ether fumes during the entire procedure. If more than a few minutes are required the patient may awaken and the operation be interrupted until he is re-anesthetized. The fire and explosion hazards must be considered when ether is used. The highest concentration of the explosive vapor is in the patient's airways which also contain a potential source of electric spark, the bronchoscope light carrier. Finally, postanesthetic nausea and vomiting are frequently observed with this technic.

Tribromethanol (avertin®) administered rectally has been recommended often. However, even in small doses, it frequently produces such marked respiratory and circulatory depression that the anesthesia becomes more hazardous than the operation. Further, one or two hours of anesthesia are provided for what is usually a brief procedure. Many of these patients have prolonged postoperative depression. The danger of aspiration and respiratory obstruction is real, particularly where specialized nursing care is inadequate. Children requiring this procedure are often in poor physical condition, from the standpoint of nutrition as well as their disease (tuberculosis, bronchiectasis, etc.). These patients are likely to have hepatic and renal damage, both of which impair the metabolic elimination of avertin®.

Leigh[4] describes a method using nitrous oxide-oxygen and curare. During the examination 50% nitrous oxide with oxygen is insufflated through the side-arm of the bronchoscope. Many endoscopists have found that insufflation of the heavy nitrous oxide produces a thick haze which interferes with adequate examination of the bronchi, particularly in

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small children and infants where the instrument used is small. It seems unwise to use a relatively long acting agent such as curare for a procedure that averages a few minutes only. There is difficulty often in introducing a needle into the infant vein. With this technic, the problem of respiratory depression, both during endoscopy as well as postoperatively, is a real one.

Thiopental (sodium pentothal®) has been used both rectally and intravenously.[5] Some of the same objections may be raised to this drug as to avertin®; particularly, respiratory depression and long postoperative sleep. A further objection is the drug's tendency to sensitize reflexes which may give rise to severe laryngospasm and bronchospasm. This is particularly undesirable in bronchoscopy where the site of operation is the very area protected by these reflexes.

After a reasonable period of trial with agents in common use, none of which was entirely satisfactory, studies were begun on a more recently available thiobarbiturate, sodium 5-allyl-5(1-methylbutyl)-2-thiobarbiturate (sodium surital®*).[6] This drug showed promise as a useful intravenous anesthetic agent in a large series of surgical procedures involving endotracheal intubation as well as several bronchoscopies in adults.[7] It is believed that the incidence of laryngospasm and bronchospasm on stimulation was somewhat less than with pentothal and that when it did occur it was less persistent. Observation and information gained from nurses' notes tend to indicate that surital® compared favorably, as far as respiratory depression and postoperative sleep were concerned, with other barbiturates employed.

Premedication

The great majority of children subjected to bronchoscopic examination have either tuberculosis or bronchiectasis, accompanied by copious secretions. These secretions are even more profuse following manipulation of the secreting tissues of the pharynx, larynx and tracheobronchial tree. Atropine or scopolamine was administered alone as well as in combination with sodium pentobarbital. These drugs were given hypodermically from 45 to 90 minutes preoperatively. The dose of belladonna drug which was based upon the weight and physical status of the child varied from 0.1 to 0.4 mg. Infants under 1 year of age were not given premedication. Both atropine and scopolamine were efficient inhibitors of secretions, providing a relatively dry field both during bronchoscopy and following manipulation. Respiratory depression was seen more often with scopolamine and somewhat less frequently with atropine. The barbiturate premedication was found to add to the respiratory depression and consequently its use was abandoned early in the study.

From the anesthesiologist's point of view, therefore, atropine is the ideal drug for premedication of these children. But the object of many of these examinations is to make a bacteriologic diagnosis. For this purpose ample secretions are required and these are not readily obtainable following atropinization. A compromise was necessary. Those patients in whom sputum specimens are required are done without any premedication. The secretions are handled mechanically by means of continual thorough suction. All other patients are given atropine. Hypoxia, of any degree, or obstruction will increase the amount of secretions, hence, adequate oxygenation via a patent airway serves as prophylaxis against secretions.

A 5% solution of surital® was found to be optimum. This concentration provided the

* Supplied by Parke, Davis & Company, Detroit.

most convenient fluid volume for the majority. More concentrated solutions provided such a small volume that much of the drug was lost during instillation, whereas more dilute solutions required larger volume which were more likely to be expelled when the rectum was distended. The drug was freshly prepared before administration and used at room temperature. Tap water and saline were found to be equally useful as diluents but solution was more readily obtained with saline. There was no evidence of mucosal irritation even when twice the recommended concentration was employed.

As in the case of premedication, the dosage of surital® was based on the weight and physical status of the individual patient. The doses used varied from 0.8 to 1.0 gm./50 lbs. body weight. The smaller amount was used in the asthenic or debilitated patient while the larger dose was reserved for the more robust or those who had not been given preanesthetic medication.

Technic

A thorough cleansing enema is given at least 4 to 6 hours prior to induction of anesthesia. The importance of this initial procedure cannot be over-emphasized. In cases where this was not done the results were often poor. The meal preceding induction of anesthesia is omitted. Premedication, if given, is administered about 45 minutes prior to the time of bronchoscopy. The patient is placed in the lateral or prone position and a small bore (18-24F) soft rubber rectal catheter is inserted about 5 to 10 cm. into the rectum. The catheter should be well lubricated with vaseline or bland jelly to facilitate its introduction. It should be fastened securely in place with adhesive tape and the buttocks taped together. The calculated dose of 5 per cent surital® in normal saline or tap water is then allowed to flow into the rectum. Usually gravity will be sufficient but gentle pressure on the syringe may be required to force the solution through the catheter. This procedure should be done carefully and slowly, since too rapid distention of the rectum with even a small volume of solution will often result in reflex expulsion. The patient is then tested from time to time to determine his response to stimuli such as touch or the eyelid reflex. In the properly prepared child the "induction period" is from 5 to 15 minutes.

A source of 100% oxygen as well as equipment necessary for controlled respiration is available at all times. As soon as the bronchoscope has been inserted into the tracheobronchial tree, the oxygen delivery tube is attached to the side-arm of the bronchoscope and 100% oxygen is insufflated at a rate of 3 to 6 l./min. throughout the procedure. This latter maneuver, while not always necessary, provides better oxygenation for the patient and seems to reduce the incidence and severity of bronchospasm by directing a constant stream of gas at the bronchi. It also provides a readily available means of controlled respiration. The operator need only rhythmically obstruct the open end of his instrument to produce full, efficient controlled or artificial respirations.

Results

The data presented here represent the experience with 200 cases. The sexes were evenly divided. There were 60% white children and 40% Negro. The age of the patients ranged from 6 months to 11 years with more than 100 in the 1 to 3 year group. The predominant diagnosis was tuberculosis. Lung abscesses, bronchiectasis and tumors of the upper respiratory tract were included also. Many children were examined to complete the diagnosis and then replaced on antibiotic or chemotherapeutic regimes with weekly or biweekly bronchoscopic follow-up. In most instances the older children were cooperative

even on repeated examinations. There was complete amnesia for the procedure except for the insertion of the rectal catheter. The period of recovery varied from a few minutes to several hours. About 60% of the patients were awake in less than one hour, about half of these having responded in the operating theatre before returning to the ward. Many reacted mildly throughout the procedure when the bronchoscope was moved. Relaxation of the jaw was considered satisfactory for the bronchoscopist in 95% of the cases. Laryngospasm was noted in 5% of the patients but at no time was it of sufficient severity to prevent atraumatic insertion of the bronchoscope. Bronchospasm occurred in 8% of the cases but only 2% of these were judged severe. There was moderate respiratory depression in one third of the patients. This was primarily a reduction of minute volume exchange with little or no effect on the respiratory rate. Occasionally apnea followed insertion of the bronchoscope but this was readily relieved by a short period of controlled respiration.

Discussion

Leigh[4] considers "hypoxia, rupture of the trachea and explosion of an anesthetic agent from short circuit in the electrical system" as the greatest dangers in bronchoscopy. To these must be added the lesser dangers of prolonged postoperative sleep, psychic trauma, nausea and vomiting, laryngospasm and drug toxicity.

None of the accepted technics for anesthesia during bronchoscopy in children meet the requirements of surgeon, anesthetist and the patient. Sodium surital® as used here has given more satisfactory results than had been experienced with previously used technics. It enables 100% oxygen to be delivered to the patient throughout the procedure. It is but moderately depressant to respiration and produces a lower incidence of severe laryngospasm or bronchospasm than other barbiturates in current usage. Induction of anesthesia is pleasant and provides amnesia so that repeated procedures are readily tolerated. Postoperative sleep is of short duration and protective reflexes return early. The explosion hazard does not exist.

It must be emphasized here that the recommended dosage applies only following a thorough cleansing enema. To be effective this procedure must be carried out at the proper time or results are quite unpredictable. Best results follow well timed atropine premedication, provided this does not frustrate the bronchoscopist's attempt to secure specimens. A smooth course is most frequently obtained when the patient reacts slightly to stimuli before endoscopy is begun. In patients who do not respond to these stimuli, postoperative respiratory depression, laryngospasm and bronchospasm are more frequently observed. It is probably advisable, therefore, to delay examining these patients until they respond mildly.

This preliminary report presenting a technic employing a new thiobarbiturate, sodium surital®, has stressed the point of view of the anesthesiologist. A further evaluation from the bronchoscopist's viewpoint will be submitted in a subsequent report.

Summary

The accepted technics for anesthesia during bronchoscopy in children have been reviewed. A technic using a new thiobarbiturate, sodium 5-allyl-5(1-methylbutyl)-2-thiobarbiturate (sodium surital®), rectally, is described. Advantages and complications of this method are discussed.

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SPANISH ABSTRACT

El Cuidado Anestesico de Lactantes y Niños Durante La Endoscopia

El presente estudio tuvo por objeto encontrar una tecnica de anestesia satisfactoria para el cirujano y con adecuado margen de seguridad para los lactantes y niños sometidos al exámen endoscopico.

Las tecnicas y agentes en uso corriente son revisadas y discutidas. Se hace un estudio con un thiobarbiturate de uso reciente llamado sodium Surital ® (sodium 5-allyl-5 (1-methylbutyl)-2-thiobarbiturate) usado en 200 casos de endoscopia en niños.

La administracion rectal de una solucion de la droga al 5% fué la forma mas optima. La dosis usado osciló entre 0.8 a 1.0 gm./50 lbs. de peso. Se describe en detalle la medicacion y tecnica preanestetica. Los autores estiman que los resultados son mas satisfactorios que los obtenidos con otras tecnicas previamente usadas. Las ventajas y complicaciones de este metodo son analizadas.

477 First Avenue

ERYTHROBLASTOSIS FETALIS

III. Prognosis in Relation to Clinical and Serologic Manifestations at Birth

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A 12 YEAR survey of erythroblastosis fetalis at the Children's Hospital, Boston, and the Boston Lying-in Hospital, which has been previously reported,[1] failed to show a favorable change in mortality over the period 1937-1948 in relation to therapeutic measures employed. On the contrary, early induction of labor during part of this period may have led to an increased risk of unfavorable outcome in live born infants. A detailed four year study[2] of erythroblastosis fetalis at the same hospitals has shown that the prognosis is closely related to maternal history, maternal titer, and length of fetal gestation, with immaturity in a live born infant increasing the likelihood of an unfavorable outcome.

The present communication will present the results of studies correlating various clinical manifestations in live born infants with the outcome of erythroblastosis fetalis. The cases studied consist of all Rh-positive infants of sensitized Rh-negative mothers seen at the Boston Lying-in Hospital from 1945 through 1948, and all admissions to the Children's Hospital for acute erythroblastosis fetalis in the years 1947 and 1948. These two series of cases have been described in some detail previously, and constitute relatively comparable groups of affected live born infants.

Erythroblastosis fetalis in a live born infant is considered, as before, to have four possible outcomes: (a) recovery without clinical disease, (b) recovery from recognized erythroblastosis fetalis of whatever severity, (c) death from erythroblastosis fetalis without clinical or pathologic signs of kernicterus and (d) kernicterus, with or without survival after the acute phase. (A surviving infant with brain damage due to kernicterus has been considered as contributing to "mortality" for purposes of this study.) Elements in the neonatal picture which will be discussed in relation to outcome are jaundice, degree of anemia at birth, degree of hepatosplenomegaly, nature and quantity of anti-Rh agglutinin in the infant's blood, and sex of the baby.

JAUNDICE

The authors' data on the relation of onset, intensity and duration of jaundice to outcome of erythroblastosis fetalis are not objective or comprehensive enough to permit statistical treatment. It has been possible, however, with the observation of many infants with this disease, to come to certain conclusions which can be regarded with considerable confidence.

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Jaundice at the moment of birth in a baby with erythroblastosis has never been seen. Yellow vernix may be seen, or yellow discoloration of the umbilical cord, but jaundice of the skin in babies with erythroblastosis fetalis must be very rare at birth, although an increase in serum bilirubin is common. Icterus may appear after birth at any interval from an hour or so to a day or more. It is not felt that early onset or rapid increase in the intensity of jaundice necessarily indicates a graver prognosis for the baby. When, however, jaundice begins to fade, regardless of its maximal intensity, by the third, fourth or fifth day, the probability that the infant will recover completely is excellent. It is the authors' impression that those babies who develop kernicterus, and who survive the first week of life, nearly always have marked jaundice, which persists by and large for a longer time than in most babies who make a satisfactory recovery without kernicterus.

TABLE 1

RELATION OF OUTCOME TO ANEMIA AT BIRTH

(Boston Lying-in Hospital, 1945–1948, Children's Hospital, 1947–1948)

	RBC count									
	Over 4 million		3–4 million		2–3 million		Less than 2 million		Unknown	
Recovered	68	91%	30	75 %	26	76%	14	59%	37	72%
Died, no kernicterus	0	00	3	7.5%	4	12%	8	33%	8	16%
Kernicterus	7	9%	7	17.5%	4	12%	2	8%	6	12%
Total	75		40		34		24		51	

ANEMIA AT BIRTH AND HEPATOSPLENOMEGALY

Table 1 gives data on the relation of outcome of erythroblastosis fetalis to degree of anemia present at birth. There is seen to be an increased likelihood of unfavorable outcome with increasing degrees of anemia which has a high degree of statistical significance, but the increased risk is seen to be due entirely to an increase in the number of deaths not associated with kernicterus. While babies with red blood cell counts under 3 million/cmm. are significantly more likely to die than those with counts above 3 million, the incidence of kernicterus is virtually independent of the degree of anemia.

TABLE 2

RELATION OF OUTCOME TO HEPATOSPLENOMEGALY

(Boston Lying-in Hospital, 1945–1948, Children's Hospital, 1947–1948)

	Degree of hepatosplenomegaly								
	None		Slight		Moderate		Marked		Unknown
Recovered	49	85%	76	87%	31	72%	9	47%	10
Died, no kernicterus	2	3%	4	5%	4	9%	7	37%	6
Kernicterus	7	12%	7	8%	8	19%	3	16%	1
Total	58		87		43		19		17

Since the degree of hepatosplenomegaly is in general closely correlated with the degree of anemia at birth, as has been shown by Diamond and Denton[3] and Vaughan,[4] it is not surprising that the degree of hepatosplenomegaly, like the severity of anemia at birth, is inversely related to the chances of recovery, as shown in table 2. Hepatosplenomegaly has been graded in these babies as "absent," "slight" (up to one fingerbreadth enlargement below the costal margins), "moderate" (two fingerbreadths) or "marked" (three fingerbreadths or more). Again it is noted that the more severe clinical manifestations carry no significant increase in risk of kernicterus, but only of death under circumstances where kernicterus is not seen.

The reasons why kernicterus bears no relationship to these other signs of erythroblastosis fetalis are not clear. It is evident (table 3) that those deaths which are not associated

TABLE 3

AGE AT DEATH IN ACUTE ERYTHROBLASTOSIS FETALIS

	Before 6 hr.	6–24 hr.	2nd day	3rd day	4th day	5–9 days
Died, no kernicterus	9	7	3	1	1	0
Died, kernicterus	0	0	4	5	6	3*

* These 3 had clinical kernicterus before the 6th day.

with kernicterus occur predominantly on the first day of life, whereas death from kernicterus is seen later in the first week of life. Neither clinical nor pathologic signs of kernicterus have been seen before the second day of life.

SEROLOGIC DATA

In general three sources of serologic information have been available as possible correlates of the severity of erythroblastosis fetalis. They are: routine Rh typing; results of Coomb's test[5] on the baby's washed red blood cells; and the examination of the baby's serum for anti-Rh antibody.

The demonstration that the infant is Rh-positive is sometimes hampered by the fact that the red blood cells are coated with a blocking antibody which interferes with the normal agglutinating activity of a typing serum. Two orders of "blocking" activity have been encountered. One is overcome when the infant's coated cells are suspended in 20% bovine albumin. The other, more complete, blocking activity, coats the infant's cells in such a manner that they are not agglutinable by anti-Rh sera even in albumin, but must be demonstrated to be Rh-positive by Coomb's test or other indirect means. There is no evidence to indicate that when either of these forms of blocking activity is demonstrated with the baby's cells, there is likely to be a more or a less severe illness than when the red blood cells are not blocked.

Routine use of the Coomb's test has indicated that nearly all Rh-positive infants of sensitized Rh-negative mothers may be expected to show coated cells to some degree. There is no evidence in this series of tests that the strength of the reaction of the baby's washed cells with an undiluted anti-human rabbit serum has any relation to the severity of disease encountered. The authors have seen many babies with strongly positive Coomb's tests who had no clinical disease, as well as a few infants in whom a negative Coomb's test was asso-

ciated with fatal erythroblastosis fetalis (kernicterus). The test is a delicate one and unless care is used in its performance the results may be unreliable. It is a valuable diagnostic aid, but attempts to gauge the severity of erythroblastosis fetalis by its use have not been promising in the authors' experience.

TABLE 4

RELATION OF OUTCOME TO SERUM ANTIBODY TITER IN BABY
(Boston Lying-in Hospital, 1945–1948)

	Titer				
	None	1:1	1:4	1:16 and over	Unknown
No clinical disease	12	3	0	0	7
Recovered	7	13	5	6	13
Died, no kernicterus	1	1	2	0	6
Kernicterus	3	1	2	2	7
Totals	23	18	9	8	33

TABLE 5

RELATION OF OUTCOME TO SERUM ANTIBODY IN BABY
(Children's Hospital, 1947–1948)

	Titer				
	None	1:1	1:4	1:16 or more	Unknown
Recovered	21	23	28	21	16
Died, no kernicterus	2	2	6	1	2
Kernicterus	3	0	6	0	2
Totals	26	25	40	22	20

Tables 4 and 5 relate the outcome of erythroblastosis fetalis to the occurrence and titer of Rh antibody in the baby's serum. Only hyperimmune antibody has been found in fetal serum. Early-immune (saline active) antibody has not been seen in either Rh-positive or Rh-negative babies of sensitized Rh-negative mothers, even when maternal antibodies active in saline were present in high titer.*

* The following synonyms are in more or less common use to designate the various types of Rh antibody:

"saline-active"="early immune"="complete"="agglutinating"

"saline-active antibody"="early immune antibody," etc.="agglutinin"

"hyperimmune"="albumin-active" or "blocking"="incomplete"

"hyperimmune antibody"="albumin-active antibody" or "blocking antibody" or "crypagglutinoid" ="incomplete antibody"="glutinin."

(The terms "blocking" and "albumin-active" are not exactly synonymous, since some albumin-active antibodies have no true blocking activity by the standard blocking test.)

The only significant observation which these data afford is that at the Boston Lying-in Hospital (table 4) the infants with no clinical disease were generally restricted to the group of babies who had no free serum antibody at birth. It was inferred that the presence of serum antibody in easily demonstrable amounts is likely to be accompanied by an illness of some clinical degree. No other significant relation of the absolute level of fetal antibody content to outcome is seen.

On the other hand, it is impressing to observe how well many babies tolerate relatively high titers of serum antibody, while others succumb to erythroblastosis fetalis when no antibody has been demonstrated in their serum. This observation suggested that it might be possible to relate the outcome of erythroblastosis fetalis to a disparity between the maternal and fetal antibody levels. A wide difference (indicated by a high ratio of maternal to fetal titer) might indicate active and detrimental fixing of antibody by fetal blood cells

TABLE 6

RELATION OF OUTCOME TO RATIO OF MATERNAL TO FETAL TITERS

(Maternal titer 1:64 or more)

	Ratio			
	64 or more*	16	4	1
Recovered	20	14	10	5
Died, no kernicterus	2	5	0	1
Kernicterus	7	6	1	0

* Baby's titer 1:1 or 0.

and possibly other tissues, while a fetal titer very near the maternal might reflect a minimal affinity of antibody for fetal tissues under prevailing conditions. This latter situation would approximate the condition seen in the Rh-negative infant of a sensitized mother, as such a baby will always have virtually the same titer of hyperimmune antibody in its serum as is present in the maternal serum.

Table 6 gives the data on maternal to fetal titer ratio for the infants of mothers with titers of 1:64 or more. There is a trend to the more frequent occurrence of unfavorable outcome (chiefly kernicterus) in the group of cases where there is a 16-fold or greater ratio of maternal to fetal titer. These figures have no statistical significance, but indicate a trend which has received considerable substantiation in the study of other cases which do not form a part of this series.

No relation between outcome of erythroblastosis fetalis and the ratio of maternal to fetal titers has been seen where the maternal titer was 1:16 or less. Such low maternal titers are generally associated with favorable outcome in the infant.

SEX OF THE INFANT

The data in table 7 indicate that in this series of cases an unfavorable result was more often seen in male infants than in female. This difference has statistical significance, indicating an inherently worse prognosis in male infants, and the difference is particularly striking with regard to the increased incidence of kernicterus in boys. Other data indicate that male infants are somewhat more likely to be stillborn than female, and that if

they are born alive they are a little more likely to have clinical illness than are female infants, but these trends are much less striking than the increased susceptibility of males to kernicterus.

Discussion

The studies herein reported present certain considerations which in live born infants with erythroblastosis fetalis give an index of the likelihood of recovery. They supplement previously reported investigations of the relation of outcome to other considerations[2] which can be evaluated before delivery of the infant.

It has been shown that there is an inverse relation of the likelihood of recovery to the

TABLE 7

Relation of Outcome to Sex of Infant

	Male		Female	
	No.	%	No.	%
Recovered	89	72	86	86
Died, no kernicterus	15	12	8	8
Kernicterus	20	16	6	6
Totals	124		100	
	$\chi^2=5.7$, $p<.05$*			

* Lines 2 and 3 combined in calculation of χ^2.

degree of anemia and hepatosplenomegaly at birth, but that the occurrence of kernicterus, which is the most frequent cause of an unfavorable outcome in live born babies with erythroblastosis fetalis, appears unrelated to these other signs. In babies with mild illness at birth, kernicterus is the only serious threat to recovery. With increasing severity of anemia and hepatosplenomegaly at birth, on the other hand, there is an increasing number of deaths, mostly within the first day of life, without associated kernicterus. These early deaths are largely responsible for the mortality of about 50% in the most severely affected group of babies (those with red blood cell counts under 2 million cells/cmm. at birth, and with marked hepatosplenomegaly).

It is not yet clear why kernicterus bears no close relation to those other clinical signs of erythroblastosis fetalis for which there can be shown a high degree of correlation with the likelihood of fatal outcome. This and other aspects of the problem of kernicterus will be discussed in detail elsewhere.[6] It is tentatively suggested that kernicterus is due to a different pathogenic mechanism from that which leads to early death in babies with severe anemia and marked hepatosplenomegaly.*

The data just presented indicate that examination of the infant's blood for antibody content is of limited value in establishing the prognosis. Absence of antibody in fetal

* Subsequent to the collection and presentation of the data contained in this group of papers, it was discovered that blood from female donors, given in relatively large amounts by means of exchange transfusion, exerted a striking life-saving effect in babies with erythroblastosis fetalis. That there was no concomitant reduction in the incidence of kernicterus was also evident. These findings may constitute additional evidence for a fundamental difference in pathologic physiology between babies who develop kernicterus and those who do not.

serum does not insure a favorable outcome, nor is a high titer of fetal antibody necessarily of serious import. There is clearly a need for further study of the variability which these data indicate may exist in the dynamic relation between Rh-positive fetal tissues and maternal anti-Rh substances. The observation that the titer ratio (mother:infant) is of greater value in prognosis than the actual level of the infant's titer requires further comment. The higher the ratio, that is to say, the greater the difference between maternal and infant titer, the worse the prognosis. This obviously applies only to maternal titer of hyperimmune antibodies, where that can be determined. Whether this is the result of greater affinity of the fetal red cells for maternal antibodis, or whether it indicates that other fetal tissues are taking up antibody, remains to be shown. Whether such tendencies, if they exist, are the result of the quality of the Rh antigen inherited by a particular baby, or of other factors, also remains to be shown, although the suspicion that hereditary constitutional factors have much to do with it receives strong support from the frequent observation that one of fraternal twins may have considerably more severe disease than the other. The authors' observations on about 18 twin pregnancies will be published at some later date.

Various observers have in the past suggested that erythroblastosis fetalis was more common in male infants than in females. During this study no significant excess of affected males has been seen, but there is a significant increase among male infants in the severity of the disease which may very largely explain why more males were thought to be affected in the days when the diagnosis rested upon clinical manifestations of an easily recognizable sort, rather than on demonstration of maternal sensitization to the Rh factor. The reasons for this disadvantage to the male infant are not clear. Future study must elucidate whether this susceptibility simply reflects the well recognized greater risk to the male infant of any illness in the newborn period, or whether it is due to some more direct relationship of sex to pathologic processes which may be active in erythroblastosis fetalis.

The observation that jaundice is rarely, if ever, present in the newly delivered baby is contrary to published reports of the clinical manifestations of erythroblastosis fetalis. Discoloration of the amniotic fluid and of the umbilical cord is not an uncommon finding. An occasional baby will have yellow vernix at birth, and in rare instances the outer layers of the epidermis, as well as the vernix, are yellow. The vernix and stained skin may be rubbed off, leaving normally colored skin. Despite careful inspection the authors have not personally observed jaundice of the scleras at the time of birth. Jaundice of the skin may develop rapidly, may be quite noticeable in an occasional baby as early as one hour of age, and is not infrequently quite pronounced by the age of 6 hours. It might be supposed that even the most careful observer, noting jaundice of the skin when he first examined a baby at the age of a few hours, and backed by the statements in the textbooks that jaundice may be present at birth, has, in summarizing his observations, indicated that he considered the baby to have been jaundiced "from birth," thus perpetuating the established error. The point is important because with the present tendency to careful observation of the babies of sensitized Rh-negative mothers from the moment of birth, and considering the importance of immediate treatment in many of these babies, it should be clearly understood that the absence of manifest jaundice at the time of birth is not a favorable sign.

No data was obtained on the serum bilirubin levels at birth in the group of cases presented here, only scattered observations that the serum was grossly icteric. It might be assumed that the bilirubin content of the baby's serum is kept relatively low in utero by diffusion through the placenta. However, the serum bilirubin is not infrequently elevated at

the moment of birth, sometimes being as high as 10 mg./100 cc. The fact that a baby with so high a serum bilirubin content may exhibit no jaundice of the skin or scleras is interesting and as yet unexplained. It is possible that jaundice of the skin depends not only on the presence of pigment in the blood serum and other body fluids, but also on some other factor. Attempts to show that exposure to light is a necessary factor in the development of jaundice are so far inconclusive. There is no reason to believe that the baby's blood serum may not be icteric at the moment of birth, at least so far as light being a necessary factor is concerned. Placental cord blood has been collected directly into black coated vacuum tubes, and degrees of jaundice found in such specimens identical with that seen in specimens collected in ordinary tubes exposed to light.

Summary

Certain clinical manifestations of erythroblastosis fetalis in live born infants have been studied in relation to outcome. The likelihood of recovery is inversely related to the degree of anemia and hepatosplenomegaly present at birth, but kernicterus, which is the chief threat to eventual complete recovery, bears no close relation to these signs. Serologic studies in newborn infants with erythroblastosis fetalis have been generally of little value in establishing a prognosis. Male infants appear to have a more severe illness and a worse prognosis than female infants. Jaundice of the skin and scleras has not been found at the time of birth in any baby with erythroblastosis fetalis.

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Spanish Abstract

Eritroblastosis Fetalis
III. El Pronostico en Relacion a las Manifestaciones Clinicas y Serologicas al Nacer

Los autores estudian ciertas manifestaciones clinicas de la eritroblastosis fetalis en el recién nacido y su relacion con el pronostico de la enfermedad. Las posibilidades de recobro estuvieron relacionada con el grado de anemia y hepatoesplenomegalia presente al nacimiento. Sin embargo el kernicterus, que es el verdadero peligro en cuanto al pronostico favorable de la enfermedad, no guardó relacion ninguna con los sintomas clinicos mencionados. Asimismo, los estudios serologicos en recién nacidos con eritroblastosis fetalis fueron de poco valor en el establecimiento del pronostico. En los varones la enfermedad parece tener un curso mas grave y un peor pronostico que en las hembras. No se observó ictericia de la piel o mucosas al momento del nacimiento en ninguno de los casos con eritroblastosis fetalis.

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CANDIDA KRUSEI AS A PATHOGEN

Case Report of an Unusual Infection of the Tonsils

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LANGENBECK, reporting a typical case of thrush in 1839, was the first to describe a Candida infection. Since then, many cases of Candidiasis, with involvement of skin, nails, mouth, vagina, bronchi, lungs, meninges, endocardium, bones and joints, have appeared in the literature.

Until fairly recently, there was chaos in the classification of this genus. The name Monilia had originally been given to an entirely different group of fungi. Conant[1] states that there are 172 synonyms in the literature for Candida albicans alone. Dodge's Medical Mycology, published in 1935,[2] lists one hundred species of Candida in the index. Opinions have varied greatly concerning the criteria to be used. Much of the disorder may be attributed to the attempts, following the extensive studies of Castellani, to classify the species on the basis of slight differences in fermentation. It is now known that carbohydrate fermentation may vary depending on the conditions under which the test is done. Furthermore, it has been shown that the complex carbohydrates used by Castellani may in themselves vary from sample to sample. Langeron[3] has also demonstrated that there may be latent organisms which under certain conditions appear in apparently pure cultures. Finally, to compound the confusion, Candida is frequently found in the upper respiratory tract, vagina, stools, and on the skin of apparently normal individuals. These organisms cannot be considered as pathogenic in any particular case, unless there is some pathologic tissue change and they are isolated repeatedly.

With some understanding of the difficulties in diagnosis and classification and the causes of past errors, mycologists today have reduced the number of species of Candida to six: albicans, Krusei, parakrusei, tropicalis, stellatoidea and Guilliermondi.

The vast majority of clinical reports, however, have described cases caused by C. albicans. In a thorough review of the literature, few cases definitely attributed to C. Krusei could be found. Carter,[4] while studying labial and vaginal flora of two hundred pregnant women, isolated C. Krusei four times, but felt that this species was of no clinical significance, for the symptomatology and physical findings always associated with C. albicans and C. stellatoidea infections were absent. Hopkins[5] cultured C. Krusei from a skin lesion but stated that it probably was not the causative agent. Robinson and Moss[6] reported on 22 cases of glossitis and perleche and, although C. Krusei was isolated from the lips in one case, they did not feel it to be pathogenic, for C. albicans was grown from finger lesions in the same patient. Benham[7] reported two cases of colitis and one of pruritis ani where C. Krusei was isolated from the stools. She felt that the etiologic relationship was doubtful. Dodge[2] mentioned a case of purulent urethritis, described by Castellani, in which C. Krusei was cultured from the discharge. He also briefly made note of a patient with a severe cough in which both C. Krusei and C. tropicalis were isolated from sputum. The final

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report in the literature which mentions C. Krusei is that by Catanei.[8] This author described a special form of glossitis from which he isolated the fungus. He studied 14 cases with infection of the mouth and found nine were caused by C. albicans.

Conant,[9] in a personal communication, stated that he had cultured C. Krusei from no case except the one that the authors are now presenting.

Case History

J. S., an 11 yr. old Puerto Rican male, was brought to the Outpatient Department because he had had frequent sore throats during the previous 2 mo. He had been seen 3 yr. previously for dermatophytosis of the left foot, palms and fingers of both hands. The foot lesion showed evidence of superimposed pyogenic infection with inguinal adenopathy. All the lesions cleared rapidly when treated with magnesium sulphate fomentations and half-strength Whitfield's ointment. Bacteriologic and mycologic studies were not made. The year following this first admission he was seen in the Outpatient Department on 3 occasions, each time with what appeared to be a nonspecific hypertrophic tonsillitis. The past history disclosed nothing else which might be considered as relevant.

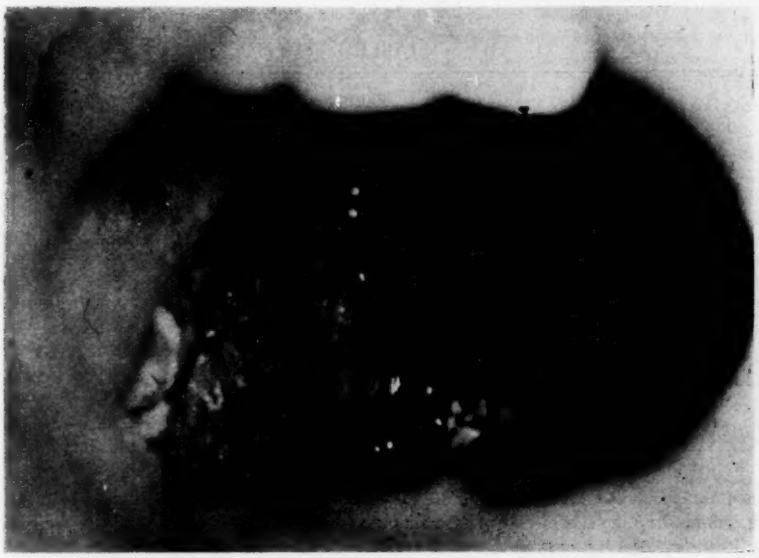

Fig. 1

Examination revealed, for the first time, whitish patches on both tonsils. There was no fever and he appeared well. It was thought that he had a follicular tonsillitis. Smear and throat cultures were made and his parents were advised to return the next day.

The smear revealed structures resembling mycelia, many gram positive and negative bacilli, a few gram positive cocci and a moderate number of spirilla and fusiform bacilli. No yeast-like bodies were seen. The culture grew out N. catarrhalis, alpha and beta streptococci and B. coli. He was not seen again until 3 wk. later, when he was immediately admitted to the hospital.

Physical examination in the hospital disclosed no abnormality except the throat findings; these, however, were unusual and striking. There were irregular, elevated, white patches covering most of both tonsils (Fig. 1). These patches seemed to be formed by a piled up, creamy exudate. However, every attempt to remove material for study by scraping with a tongue depressor was unsuccessful because of the almost stony hardness of the masses, and it was necessary each time to break off small portions with a finger forceps. The surrounding areas were only slightly reddened.

The lymph nodes were not enlarged. The liver and spleen were not palpable. The lungs were clear. There was a short musical apical systolic murmur interpreted as functional.

The initial laboratory studies gave the following results: Throat smear and culture—revealed streptococci in long chains, fusiform bacilli and an unidentified fungus. Blood count—RBC, 5.3 million/cmm., Hgb., 12 gr./100 cc., WBC, 6.3 thousand/cmm. with 70% polymorphonuclears, 25% lymphocytes, 4% monocytes, 1% eosinophiles. Urine—negative. Serology—negative. Tuberculin patch test—negative. Sheep heterophile test—negative (1/28). Sickling—negative. Roentgenogram of the heart and lungs was normal.

Because of the unusual appearance and long history, a fungus infection was suspected and, when confirmed by the initial culture, a portion of the whitish substance was broken off and mycologic studies were made. Cultures on dextrose, maltose and corn meal agars and dextrose broth showed the fungus to have the morphologic and fermentative characteristics of C. Krusei. A flat dry growth was

TABLE 1

Penicillin-G crystalline	400,000 U. q12h IM 400,000 U. q12h IM 500,000 U. q12h IM	4/7 to 4/14 6/14 to 6/17 7/23 to 8/12
Sodium bicarbonate	Gargles 3 times/day	4/14 to 4/22
2% Aqueous gentian violet	2 times/day locally	4/24 to 5/10
Mandl's solution	2 times/day locally	5/10 to 5/28
10% Mapharsen in saline	q2h locally	5/29 to 6/10
10% Sodium perborate in glycerine	3 times/day locally	6/11 to 6/17
2% Aqueous gentian violet	3 times/day locally	6/25 to 7/5
20% Buffered sodium caprylate	3 times/day locally	7/6 to 8/10
½ Strength sopronol	3 times/day locally	8/11 to 8/12
Full strength sopronol	3 times/day locally	8/13 to 9/13
Sat. sol. pot. iodide	10 drops 3 times/day by mouth	9/7 to 9/19
Roentgen ray	100 R.U. to each side of neck once/wk.	10/19 to 12/17

obtained on Sabouraud's dextrose agar while the dextrose broth produced a typical wide surface film which continued up the side of tube. The mycelium gave the impression of crossed sticks when grown in the corn meal agar. On maltose agar there was no production of either acid or gas, both of which are always found when C. albicans grows in this media. A repetition of the tests with a second specimen gave identical results. Because most texts and articles state that C. Krusei is nonpathogenic, a third specimen was taken from the tonsil and sent to Dr. Norman Conant of Duke University. He confirmed the findings of this laboratory.

Immediately after admission, penicillin therapy, 400,000 units every 12 hr., was started and continued for 1 wk. until the initial culture studies were completed. The appearance of the throat was not changed by this treatment. When a definite diagnosis of Candida infection had been made local applications of 2% aqueous gentian violet were instituted. There was no amelioration after 17 days of this therapy. During the next 2 mo. many drugs were tried which had previously been reported in the literature as giving good results when used against mycotic infections of the mucous membranes (table 1). However at the end of this period the white patches appeared deeper and more widespread.

The entire course during these 1st 2 mo. of hospitalization had been uneventful, except for a complaint of right submandibular pain the 54th hospital day. This lasted for only 24 hr., but examination at that time disclosed 2 pea-sized tender lymph nodes in the right submandibular region and 1 nontender node on the left. They had not been present on admission.

However, 1 mo. later, the patient, for the first time since admission, complained of a sore throat, and his temperature rose to 38.8° C. Penicillin, 400,000 u. every 12 hr., by intramuscular injection, was added to the local therapy he was receiving at the time (10% sodium perborate in glycerine) and he rapidly became asymptomatic. During this episode there was no apparent change in the appearance

of the throat. It may be noted here that this was the only febrile period during the long hospitalization, except for a few hours on the day following the first roentgen treatment.

The entire gamut of older antimycotic drugs having been used with no success, but rather with some progression of the lesions, it was decided to try one of the new fatty acid preparations. A 20% buffered solution of sodium caprylate had been used by Keeney[10] against resistant C. albicans infections with excellent results. Starting 3½ mo. after admission, this preparation was applied to the tonsils and pharyngeal mucosa with cotton applicators 3 times daily. This was the first type of treatment to have any effect on the pathologic process, causing a slight retrogression of the lesions. However, after more than a month of this therapy, it was obvious that there was again slow but progressive encroachment on the remaining apparently still normal areas of tonsillar tissue.

Following this, a mixture of sodium propionate and sodium caprylate (Sopronol-Wyeth) was applied in a similar manner with even less success. After a month of this treatment, the major part of the tonsillar tissue had been destroyed by the fungus.

After a short course of potassium iodide by mouth, which had no effect, it was decided to try roentgen therapy.[11] The patient was given 100 RU to each side of the neck and this was repeated weekly for 8 wk. After 16 days of roentgen therapy, there was marked improvement, and after the 38th day of treatment, the lesions had almost disappeared. However, on the 45th day of roentgen therapy, a new patch appeared on the tonsil and in the next 10 days grew appreciably.

Therefore, the entire medical therapeutic armamentarium having been exhausted, the boy having been hospitalized for many months, but the growth still as vigorous as ever, a tonsillectomy, which had been rejected on admission, was finally performed. Two days later, after 9 mo. of hospitalization, the patient was discharged to the follow-up clinic. For these last 2 days and for 2 days prior to the operation, he had been receiving sulfadiazine prophylactically.

The tissue removed at operation was sent to the laboratory, but through an oversight, no culture was made, and only hematoxylineosin stain was used. This technic probably explains why the pathologic report stated that only granulomatous tissue was seen.

Throughout the months of hospitalization, the patient's general condition had remained good. He was always up and about, ate well, and took part in all activities. His weight, which had been 36.7 kg. on admission, had increased to 39.5 kg. at the time of discharge.

The patient was last seen in the Outpatient Department approximately 1 yr. after operation. There had been no recurrence of the fungus infection. He looked very well and had gained 4.1 kg. since discharge from the hospital.

Comment

The great preponderance of cases reported due to C. albicans is not the only reason for the widespread belief that this species alone is pathogenic. Attempts to correlate animal experiments with clinical infection have also been misleading. C. albicans is the only organism in this genus which will kill a rabbit when injected intravenously. Recently Meyer and Ordal[12] studied the pathogenicity of Candida for chick embryos. They showed that C. albicans and C. stellatoidea killed 100% of the embryos, C. tropicalis caused lesions in 100% but only killed 50%, while C. Krusei and C. parakrusei did not produce lesions. However, of the five cases of mycotic endocarditis, all in drug addicts, reported up to date, four have been caused by C. parakrusei.[13]

That the presented case is a true C. Krusei infection cannot be doubted. Twice, from separate specimens, the laboratory obtained the characteristic growths in Sabouraud's dextrose agar and broth, and the "crossed stick" mycelia on corn meal agar; twice, attempts at acid or gas production by fermentation of maltose failed. These characteristics definitely identified the causative agent as C. Krusei and not C. albicans. However, because of the frequency of the statement in the medical literature that C. albicans is the only pathogenic species, this in spite of the authentic reports on stellatoidea and parakrusei infections, another part of the specimen was sent to Dr. Norman Conant's laboratory. Again it was identified as C. Krusei.

Another common misconception is that Candida infections, except during the newborn period, are seen only in the seriously ill or debilitated. The general condition of the patient reported here was always good. Tumulty and Michael[14] described 18 cases of Candidiasis, all in well nourished soldiers, otherwise in good health. Lehndorff,[15] in his article "Parallergy," discussed the frequency of C. albicans infection following serum sickness or other allergic manifestations.

In differential diagnosis of throat infections, Candidiasis must also be considered along with the more commonly seen conditions, such as diphtheria, hemolytic streptococcus and Vincent's infections, infectious mononucleosis and occasionally secondary lues.

It should be emphasized that the lesions presented themselves in this case as stony hard, irregular, grey-white patches. When confronted with pathology of this type, a fungus is to be suspected, but the exact final diagnosis can only be made by cultures.

Early surgical extirpation is recommended when the lesions are localized to the tonsils and there is not an immediate favorable response to antimycotic therapy.

Summary

A case of an infection of the tonsils due to C. Krusei is presented. A review of the literature reveals this type of infection as extremely rare.

Almost all the reported successful medical remedies for the treatment of Candidiasis were tried without results. Permanent cure was obtained finally by surgery.

Acknowledgment

The authors are indebted to Dr. Norman Conant of Duke University for his kind assistance in confirming the identity of the causative organism and to Dr. H. Marks of Goldwater Memorial Hospital for his cooperation in planning and carrying out the roentgen therapy.

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SPANISH ABSTRACT

La Patogenicidad de la Candida Krusei
Reporte de un Caso con una Infeccion en las Amigdalas

Se reporta un caso de infeccion de las amigdalas causada por la Candida Krusei. Un estudio de la literatura medica reveló que este tipo de infeccion es extremadamente raro. Practicamente, todos los remedios reportados como satisfactorios contra la candidiasis fueron tratados en este caso sin resultado alguno. Finalmente una cura permanente fué obtenida mediante la extirpacion quirurgica de las amigdalas.

Flower and Fifth Avenue Hospitals

ABSORPTION OF FAT AND VITAMIN A IN PREMATURE INFANTS

II. Effect of Particle Size on the Absorption of These Substances

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New York City

INTEREST in the absorption of fat and fat soluble vitamins in various conditions associated with steatorrhea in childhood, e.g., cystic fibrosis of the pancreas, celiac syndrome and diarrhea, has concerned the present authors for some time and studies[1-4] have been undertaken to improve the defective absorption in these states. These studies are now being extended to the premature infant who, as is well known, tends to absorb fat poorly, his average retention on butter fat being 65 to 70% of the intake and often less, as contrasted with 85 to 95% for the full term infant. In a recent communication[5] the authors have shown that increasing the fat intake of the premature infant will overcome the excessive loss of fat, the percentage absorption remaining virtually constant. It is also clear from the authors' work and that of others that increasing the intake of vitamin A will increase its absorption.

The present study was designed to evaluate the effect of particle size of fat and vitamin A on the absorption of these factors. The importance of particle size in lipid absorption has been emphasized particularly by the studies of Frazer[6] who demonstrated that unhydrolyzed fats and even hydrocarbons were absorbed without great difficulty when the size of the particles was reduced to 0.5 micron or less. A previous study[7] by one of the present authors had shown that the absorption of vitamin A was greatly influenced by the size of the particles. This was found by the authors to be the case in animals and in normal infants, and in cystic fibrosis of the pancreas by May[8] as well as the present authors. When the particle size of the vehicle was large (oily solution) the absorption of vitamin A was poor; when the particles were small (submicroscopic aqueous dispersion) the absorption was excellent, and with particles of intermediate size (emulsions of microscopic dimensions) absorption levels were between those observed with the aqueous and oily products. Studies of fat absorption in normal infants[9] had failed to show the need of or benefit from emulsification, but it remained to be shown whether this procedure could be beneficial in steatorrheas such as that of the premature infant.

EXPERIMENTAL PROCEDURE

Six healthy premature infants ranging in age from 6 to 40 days and weighing between 1340 and 1910 gm. were selected for this study. These infants were generally studied on 3 experimental periods of 4 days each. The diet during the first and third periods was the same and consisted of butter fat homogenized† in skimmed milk, the resulting concentration of fat being 3 and 5%. The feeding

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* Mead Johnson Fellow in Pediatrics.

† This homogenization was carried out in a dairy homogenizer by the staff of the National Dairy Products Research Laboratories, to whom the authors acknowledge their indebtedness.

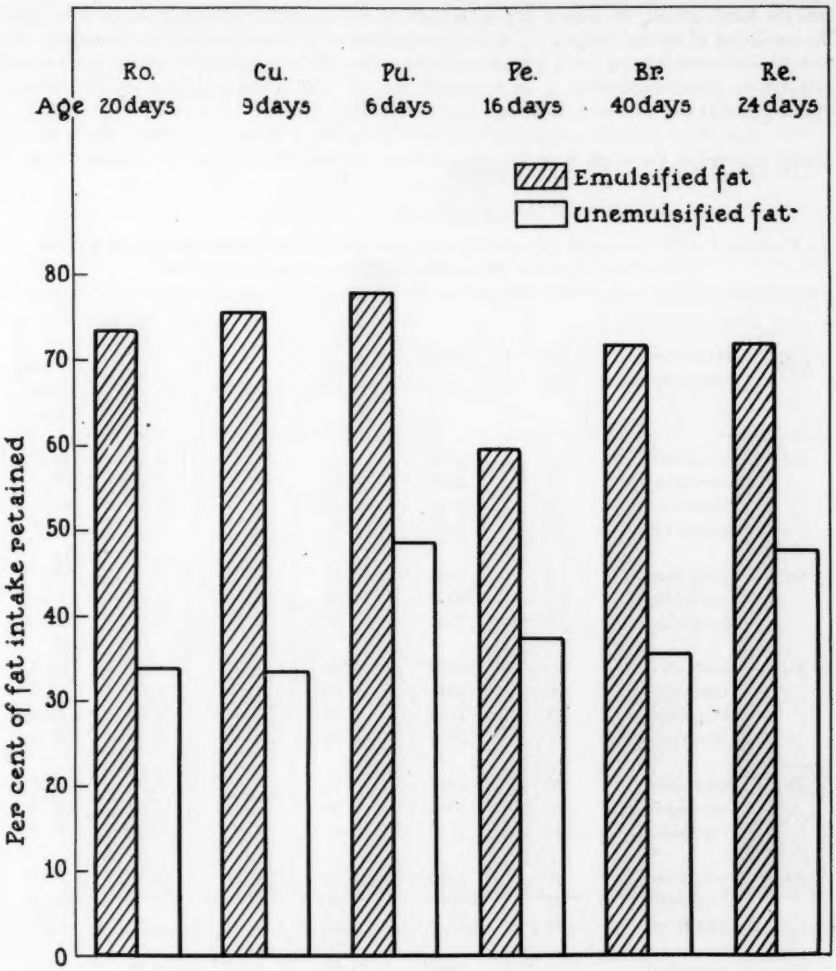

CHART 1. Retention of fat following administration of emulsified and unemulsified butter fat in 6 premature infants.

supplied 120 calories/kg. body weight. At the same time a fish liver oil concentrate (oleum percomorphum) was homogenized into the milk, 5 cc. of the oil being used for each quart of milk. Thus, the infants received during the first and third periods not only emulsified butter fat but also an emulsified preparation of vitamin A. The fat globules resulting from the homogenizing procedure reached a maximum of 2 microns in diameter.

In the second period the feedings were identical with those in periods I and III with the exception that the infants received all their fat in unemulsified form. The fat was administered separately and was fed by gavage or by dropper. Early in the investigation melted butter was given in a single feeding by gavage but later this procedure was changed and the required amount of butter was fed by dropper in 6 divided doses immediately prior to the formula feedings which consisted of skimmed milk, karo syrup and water. The fish liver oil preparation during the second period was fed directly

into the baby's mouth, 10 drops a day. (The diets in the 3 periods were therefore the same from the standpoint of the percentage of fat fed and the number of calories given, and the amount of vitamin A administered during the 3 periods was comparable. However, the butter fat and fish liver oil preparations were administered in an emulsified state in milk during periods I and III, whereas during period II they were given separately in an unemulsified form.)

The stools were collected during periods I and III on plastic diapers from which they could be readily removed as the stools were well formed when the emulsified fat was fed. During period II

TABLE 1

DATA ON FAT RETENTION IN 6 PREMATURE INFANTS FOLLOWING ADMINISTRATION OF BUTTER FAT EMULSIFIED IN MILK AND OF UNEMULSIFIED BUTTER FAT

Case	Manner of fat administration	Age days	Wt. gm.	Fat intake gm./day	Fecal fat gm./day	Fat retention	
						gm./day	Per cent intake retained
Ro	emulsified	20	1810	6.86	1.11	5.75	84.0
	unemulsified	24	2000	6.96	4.81	2.15	30.9
	emulsified	28	2160	6.96	2.20	4.76	63.4
	unemulsified	32	2180	6.96	4.37	2.59	37.2
Cu	emulsified	9	1760	6.42	1.98	4.44	69.6
	unemulsified	13	2000	6.52	4.35	2.17	33.3
	emulsified	17	2090	6.52	1.33	5.19	79.6
Pu	emulsified	6	1870	6.96	1.38	5.58	80.2
	unemulsified	10	2040	6.96	4.69	2.27	32.6
	emulsified	14	2120	6.96	1.68	5.28	75.9
	unemulsified	18	2190	6.96	2.46	4.50	64.6
Pe	emulsified	16	1910	11.92	4.56	7.36	61.7
	unemulsified	20	2070	9.00	5.64	3.36	37.4
	emulsified	24	2120	11.92	5.12	6.80	57.0
Br	emulsified	40	1340	7.15	2.11	5.04	70.1
	unemulsified	44	1420	5.40	3.43	1.97	36.4
	emulsified	48	1630	7.15	1.94	5.21	72.9
Re	emulsified	24	1900	11.92	3.13	8.79	73.6
	unemulsified	28	2090	9.00	4.71	4.29	47.6
	emulsified	32	2210	11.92	3.53	8.39	70.3

when the unemulsified fat was administered there was a tendency for the stools to be loose and complete recovery from the plastic diaper was impossible. Therefore during this period the infants were placed on metabolism mattresses so that all fecal evacuations fell directly into collection jars. The beginning and the end of each period was marked in the stool by previously ingested carmine.

Aliquots were taken from stools collected during each 4 day period and assayed for vitamin A by a modified Carr-Price procedure.* The remainder of the stool was dried and fat was determined by the method of Tidwell and Holt.[30] The fat and vitamin A intake were determined by assaying aliquots of the homogenized milk fed during periods I and III, whereas during period II the fat content of the unemulsified butter and the vitamin A content of the fish liver oil were assayed directly.

* Described by Lewis, Bodansky and Haig.[1]

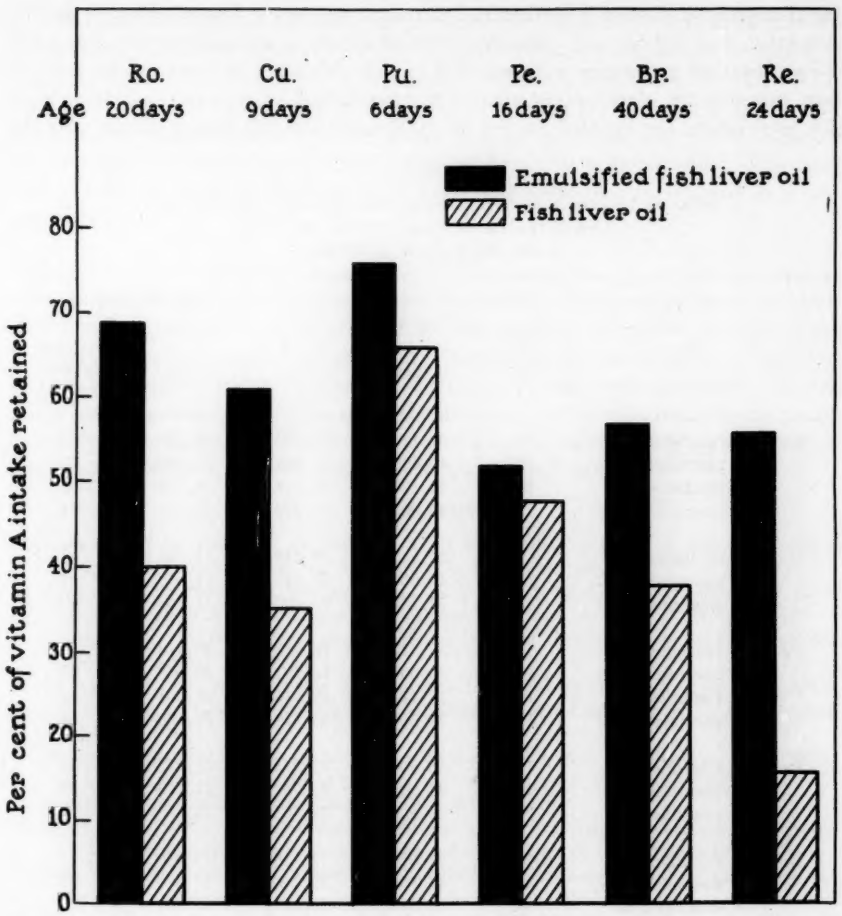

CHART 2. Retention of vitamin A following administration of fish liver oil preparation emulsified in milk and of fish liver oil preparation in 6 premature infants.

RESULTS

The effect of the emulsification of fat on the absorption of this substance is clearly shown in chart 1 and by the data in table 1. It will be noted that in all the six premature infants the absorption of butter fat was much better when it was emulsified than when it was given in an unemulsified state. The percentage absorption of fat is recorded in table 1 where it may be noted that in two instances a fourth period was employed during which unemulsified fat was administered. The data demonstrate again that when the particle of fat is reduced in size by an homogenizing apparatus the absorption of fat is far better than when this substance is administered as melted butter. The average absorption of emulsified butter fat is 71.5%, whereas the absorption of unemulsified butter fat is only 40%.

The effect of emulsification of a fish liver oil preparation (oleum percomorphum) on

the absorption of vitamin A is illustrated in chart 2 and by the data in table 2. It will be noted that, as in the case of fat, the absorption of vitamin A was definitely superior when the fish liver oil preparation was emulsified in milk. In table 2, the data for the daily intake, excretion and absorption of vitamin A, administered either as an emulsion or as an oily preparation, are recorded. In five of six instances the data clearly indicate that the

TABLE 2

DATA ON VITAMIN A RETENTION IN 6 PREMATURE INFANTS FOLLOWING ADMINISTRATION OF FISH LIVER OIL AND FISH LIVER OIL EMULSIFIED IN MILK

Case	Vit. A fed	Age days	Vit. A intake u./day	Fecal Vit. A u./day	Vit. A retention	
					u./day	Per cent intake retained
Ro	emulsified oil	20	57,120	12,608	44,512	78
	unemulsified oil	24	40,000	21,605	18,398	46
	emulsified oil	28	57,120	22,374	34,746	61
	unemulsified oil	32	40,000	26,270	13,730	34
Cu	emulsified oil	9	53,550	19,848	33,702	63
	unemulsified oil	13	40,000	25,911	14,089	35
	emulsified oil	17	53,550	21,401	32,149	60
Pu	emulsified oil	6	57,120	16,950	40,170	70
	unemulsified oil	10	40,000	13,991	26,009	65
	emulsified oil	14	57,120	10,915	46,205	83
	unemulsified oil	18	40,000	13,320	26,680	67
Pe	emulsified oil	16	46,800	21,575	25,225	54
	unemulsified oil	20	45,500	23,787	21,713	48
	emulsified oil	24	46,800	23,205	23,595	51
Br	emulsified oil	40	28,080	12,150	15,930	57
	unemulsified oil	44	45,500	28,140	17,360	38
	emulsified oil	48	28,080	12,009	16,071	57
Re	emulsified oil	24	46,800	22,222	24,578	53
	unemulsified oil	28	45,500	38,178	7,322	16
	emulsified oil	32	46,800	18,732	28,068	60

absorption of vitamin A was enhanced when the emulsified fish liver oil preparation was administered. The average retention of vitamin A given in the emulsified state was 63%, whereas given unemulsified, i.e., in its oily form, the absorption was only 43%. Thus, the absorption of vitamin A was more or less parallel to the absorption of fat and depended upon the size of the fat globule.

COMMENT

The results of this investigation clearly indicate that particle size plays an important role in the absorption of fat and vitamin A in the premature infant. The beneficial effect of homogenization as compared to an unemulsified preparation is striking. It should be pointed out, moreover, that maximum reduction of particle size was not achieved in the preparations used and it is reasonable to expect that even further improvement can be

obtained from more refined emulsification procedures. In the authors' previous clinical and experimental studies[7] on vitamin A_1 it may be recalled that fine aqueous dispersions were distinctly superior to homogenized preparations, a difference which may also hold for the premature infant. The possibility of dispersing the dietary fat more finely than is now attainable by homogenization likewise offers hope of improved absorption. There are practical difficulties because of the large quantity of material to be emulsified. This problem is, however, being pursued and it is hoped that results can be reported in a later communication.

Summary

Six premature infants were fed butter fat and a vitamin A preparation in an emulsified and in an unemulsified form in order to ascertain whether a reduction in particle size facilitates the absorption of these substances. The results of this investigation indicate that by reducing the particle size of fat and of an oily preparation containing vitamin A to 1 to 2 microns by an homogenizing apparatus the absorption of fat and vitamin A was greatly enhanced. Thus, the particle size of fat and of vitamin A preparations plays an important role in the absorption of these substances in premature infants.

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Spanish Abstract

La Absorcion de Grasas y Vitamina A en Niños Prematuros
II. Los efectos del tamaño de particula en la absorcion de estas substancias

Seis niños prematuros fueron alimentados con mantequilla y una preparacion de Vitamina A sin emulsificar y luego en forma emulsificada, para de esta forma poder comprobar si la reducción en el tamaño de las particulas facilita la mejor absorcion de estas substancias. Los resultados de esta investigacion indicó que mediante la reducción del tamaño de las particulas de grasas (mantequilla) o de una preparacion de aceite conteniendo vitamina A a un tamaño de 1 a 2 micrones, mediante un aparato especial de homogenizar, la absorcion de las grasas es notablemente aumentada. Se estima que el tamaño de la particula en grasas (mantequilla) o en preparaciones de vitamina A juega un papel muy importante en la absorcion de estas substancias en niños prematuros.

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Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

REPORT OF THE EXECUTIVE BOARD MEETING

Chicago—June 18, 1950

A MEETING of the Executive Board of the American Academy of Pediatrics was held at the Palmer House, Chicago, June 18, 1950. The meeting convened at 9:15 A.M., Dr. Edward B. Shaw, President, presiding.

The following were present: Drs. Edward B. Shaw, Paul W. Beaven, Clifford G. Grulee, Edgar E. Martmer, Harry Bakwin, Philip S. Barba, Crawford Bost, Roger L. J. Kennedy, Arthur H. London, Jr., Thomas J. McElhenney, Oliver L. Stringfield and Edward A. Wishropp.

Dr. Gerti Dooneief was granted a year's extension of her leave of absence.

After discussion of a letter from the White House Conference on Children and Youth, it was decided to give a donation of $100.00 to this project.

Dr. Martmer read a letter from Mr. H. E. O. Heineman of Pet Milk Company asking for some copies of the current News-Letter to be distributed to their detail men. After discussion, Dr. Martmer was authorized to write him granting permission to distribute the News-Letter to their detail men provided it was not used for publicity purposes.

The budget for the ICH Committee, as submitted by Dr. Warren R. Sisson, was approved after exhaustive discussion by the Executive Board.

There was much discussion as to whether the Budget Committee should be renamed the "Budget and Finance Committee." The final decision was left for the Fall meeting.

Dr. Grulee reported on his trip to New York with respect to the funds received from the Babe Ruth Foundation which were administered by the American Cancer Society and contributed to the Tumor Registry Committee under Dr. Harold W. Dargeon. No definite commitment was received.

There was long discussion on the subject of the budget for PEDIATRICS. The budget was finally passed with the provision for a slight increase in the salary of the Editor-in-Chief.

Mr. Charles C Thomas withdrew a proposal of a 10 year extension of contract with modifications which had been proposed a few months before.

The President reported on a meeting with the Editorial Board and the discussion of the method of appointment of the members of that Board. The Editorial Board was instructed that when there was a vacancy on the Board as the result of expiration of term or other cause 2 names at least were to be presented to the Executive Board for choice.

Dr. Martmer was instructed to investigate the advisability and cost of a professional examination of the financial situation of PEDIATRICS and to report back to the Executive Board before definite action was taken.

The budget for the Central Office was presented and after discussion approved. A contingency fund of $5000 was included for the replacement of equipment and the purchase of new equipment.

Dr. Grulee was granted an extension of his salary at the present figure until his retirement and when reorganization takes place he will automatically carry the title of Executive Secretary.

It was moved, seconded and carried that Dr. Martmer continue as Assistant Secretary with the same salary until the Annual Meeting.

The question of a secretarial expense account for the President was discussed and it was decided that $1000 was to be added to the budget for this purpose.

The Secretary-Treasurer was empowered to pay to the President $127 for secretarial fees previous to July 1, 1950.

There was some discussion then of funds to be made available for the Vice-President but nothing definite was done about it.

Dr. John P. Hubbard, through correspondence, reported that the Commonwealth Fund would not take the "Interpretive Report" of the Child Health Survey for publication. This left the matter entirely in the hands of the Committee formerly appointed consisting of: Dr. Warren R. Sisson, Dr. Hugh McCulloch and the Secretary. It is altogether likely that some arrangement will be made to have this published as a supplement in PEDIATRICS.*

The afternoon session began with a report by Dr. Martmer concerning the films for the movie theater for the Annual Meeting and discussion of the program.

Then the question of an Areal meeting for 1951 was brought up and it was left to the Secretary as to the choice between New Orleans, New York and Cincinnati.†

The rest of the afternoon was taken up with a closed session of the Executive Board for which no report is available.

* The Report appeared as a Supplement to the September issue of PEDIATRICS.

† Cincinnati has been selected.

Round Table Discussion

PRESENT DAY CONCEPTS OF ALLERGY

JEROME GLASER, M.D., Rochester, N.Y., Chairman; JOSEPH H. FRIES, M.D., Brooklyn; JULIA BAKER, M.D., Mexico, D. F., Mexico; ARTHUR J. HORESH, M.D., Cleveland; SUSAN C. DEES, M.D., Durham N.C.; HAROLD I. LECKS, M.D., Philadelphia

JULIAN GRAUBARTH, M.D., New Orleans, and HYMAN A. SLESINGER, M.D., Windber, Pa., *Secretaries*

GASTROINTESTINAL AND FOOD ALLERGY IN INFANCY AND CHILDHOOD

Chairman Glaser: By gastrointestinal allergy is meant an allergic reaction in an organ of the gastrointestinal tract. While gastrointestinal allergy most commonly occurs from foods, it may also be produced by allergens from other sources, as for example the patient with ulcerative colitis described by Rowe whose condition was shown to be due to the inhalation of pollen. By food allergy is meant an allergic reaction caused by a food, regardless of the tissue in which the reaction occurs; thus atopic dermatitis of infants may be the result of an allergy to egg, for example.

McGee believes that the first allergic reaction to occur in the human being may occur in utero, most commonly as a manifestation of allergy to food ingested by the mother, in the form of "fetal hiccoughs." While such spasmodic movements of the fetus are well authenticated, the general acceptance of McGee's views awaits confirmation by other investigators. The first allergic manifestation to occur in the newborn human being is urticaria. The urticarial wheals seen in the newborn infant, however, may not necessarily be due to an allergic reaction per se but may be due to the unstable vasomotor regulating mechanism of the newborn child. However, in many instances the urticarial wheals are produced by substances ingested by the infant or carried through the mother's breast milk when the infant nurses.

Colic or gastroenterospasm is the first clinical manifestation of allergy in the newborn human being of which the parents may complain. This commonly starts during the first weeks of life and usually terminates regardless of therapy by the time the infant is 3 months of age. In other words, it occurs when the gastrointestinal tract is being introduced to a variety of foreign proteins as cow milk or other substances which can reach the infant in the mother's breast milk. Not all cases of colic and perhaps not the majority can be demonstrated to be of allergic origin but many instances are. It has further been observed that in proportion as a child suffers from colic so is he likely to suffer from subsequent manifestations of allergy in later infancy and childhood. However, the failure to demonstrate the etiology of colic in many cases has led to a study of this subject from various points of view. One of the most interesting is that of Pierce who observed the delayed onset of colic in premature infants. He feels that the common type of colic, starting at the age of 2 or 3 weeks and terminating spontaneously when the infant is about 3 months of age, could be most adequately explained by considering that a developmental factor is at least partially responsible for the disturbed physiologic mechanism which causes the symptom complex. He reported the appearance of what seemed to be typical colic in a number of premature infants and observed that its onset was delayed for a period approximately proportional to the degree of prematurity.

There appears to be but little doubt that pylorospasm may be due to food allergy. The most interesting observations in this connection were reported by Balyeat and Pounders who cited the instance of a boy who was first operated upon because of a diagnosis of pyloric stenosis at the age of 4 weeks. No evidence of this condition was found at operation. The symptoms recurred and the boy was again operated upon with this diagnosis at the age of 3 years, and at this operation nothing abnormal was found. The boy developed eczema while convalescing and on skin testing he reacted to various foods of which egg and milk were clinically the most important. On elimination of these foods his abdominal symptoms disappeared in 24 hours and the eczema in a week. Since pylorospasm

may be due to allergy, it is tempting to speculate that hypertrophic pyloric stenosis which appears to be the result of long continued pylorospasm may also be due to allergy. If so, it must be due to some allergen which begins to act on the pylorus in utero. Evidence in support of this theory is, however, lacking.

ROENTGEN OBSERVATIONS ON CHILDREN WITH GASTROINTESTINAL ALLERGY TO FOODS

Dr. Joseph H. Fries: This discussion is an abstract of a series of reports dealing with roentgenographic studies of children exhibiting gastrointestinal disturbances resulting from the ingestion of foods to which they were allergic.

A group of 30 allergic children were studied. These children ranged in age from 4 to 14 years. All had repeatedly exhibited gastrointestinal disturbances within a few minutes after the ingestion of certain foods. The allergic nature of these reactions was confirmed in a majority by cutaneous testing.

Comparative roentgenographic studies, including fluoroscopy, were made. In a control series, a 50% suspension of plain barium sulfate in water was used. In the study with allergen, the antigen—in all instances a specific food—was added to the barium mixture in amounts determined by previous clinical trials to be sufficient to produce gastrointestinal symptoms. Quantities varied from 2 gm. to 40 gm. Allergenic substances employed were egg (most frequent), fish, milk, nut, oat, wheat and corn.

To obviate any nervous or psychic factor, the allergen was added to the barium mixture without the knowledge of the patient. The barium usually disguised the taste.

In general, in the 30 subjects observed, immediate roentgenograms with allergen-containing barium recorded the patterns of a hypotonic stomach with delayed emptying in 19 subjects. RGs taken at the 6 hour period in 20 subjects revealed gastric retention in 11. The approximate amount of such retention varied up to 66%.

Alterations in the small intestinal tract were infrequent and, when present, seemed to be accompanied by fairly severe symptoms. Increased segmentation was observed in 5.

As the allergen-barium progressed through the colon, there was evidence of hypertonicity of the transverse region with a narrowed shadow, irregular haustrations, and increased sulci. At 24 and 48 hours there seemed to be a tendency toward delayed evacuation of the colon in the allergen series.

Seventeen subjects were studied after the rectal administration of barium and allergen-barium mixtures. Eleven children showed definite evidences of abnormal reactions shortly after the introduction of the allergen-barium mixture. Constriction of the colon, which was not present in the controls, was observed in 10. Dilatation of the entire colon was seen in 1 child. Such changes were almost always accompanied by severe tenesmus.

The roentgenographic technic employed has made possible the visualization of the reactive allergic alimentary tract in the presence of a specific allergen.

While their findings are not necessarily pathognomonic, their presence should suggest the possibility of allergic gastrointestinal disturbances, particularly when other allergic manifestations are present.

VARIED DIET TO PREVENT FOOD ALLERGY AT HIGH ALTITUDES

Dr. Julia Baker: At the Round Table on allergy, data were presented indicating that food allergies that do not exist at low altitudes develop at the high altitude of Mexico City. There is limited space, so I shall merely state the findings, i.e., 50% of the children are potentially allergic and may react to foods under unfavorable conditions. The application of the work in Mexico City to populations at lower altitudes is that the same system of feeding may be used with definitely allergic children to control their food reactions, with children of allergic families to prevent the development of symptoms, and in cases of anorexia unexplained on any other basis, which may be subacute allergy.

Varying the diet, which has been a routine practice of mine for 4 years, is the basis for this discussion. Although not very much has been published on the subject, certainly other workers have recommended this plan.

In the first place it is well to dispense with sheets giving menus for the day, such as 8 A.M. orange juice, 10 A.M. egg and bottle, 2 P.M., etc. These are convenient to use, but the mother falls

into the habit of giving the same food day after day. In place of these menus, I give a page listing foods which may be used for 2 days or, better, alternately every 3 days. For example, cereals are listed as oatmeal, cornmeal mush, rice flour gruel or cream of rice, barley cereal and tapioca. Mixtures of cereals made of oats, wheat and corn I do not recommend because there is no opportunity to rest from any of these cereals. By using the simple preparations the baby gets a rest from any one particular cereal if he is willing to take at least 4 cereals and alternate them. The same plan is effective for fruits and vegetables, and as there is more variety of these products it is easier to vary them. Orange juice is not given at all in the early months, ascorbic acid being substituted. When orange juice is begun, it is given alternating with tomato juice and other fruit juices, and ascorbic acid in tablet form is continued. This is a much wiser procedure in my experience than insisting on orange juice every day. Cereals are given at 3 months of age, cooked fruits at 4 months, vegetables at 5 months and meat at 5 or 6 months. By beginning meat early, milk does not have to be increased to supply the required amount of protein. Lamb, beef, chicken and liver are alternated. Tuna fish and sardines may be well tolerated and given once a week. Percomorphum and ergosterol are alternated weekly: intolerance to these oils develops much less frequently if they are alternated in this way. Eggs are not given until the end of the first year, and then only the hard boiled yolk once or twice a week. Wheat is not given as a cereal, but at about 9 or 10 months of age it is given as toast once or twice a week.

Thus the main point of this plan to prevent development of food allergies is to vary all foods, and not to give any one more than once or twice a week, with the exception of milk, which unfortunately is difficult to substitute. Milk sensitivity then is my main problem. Babies who have trouble with milk can sometimes be fed for quite a while on 3 days of Nutramigen and 3 days of Sobee, which is applying the same principle. No meat milks are on the market in Mexico, but home made substitutes may be used.

It is possible that if the incidence of allergy is really increasing rather than being more frequently diagnosed, this state of affairs may be related to education regarding nutrition. People in general believe that feeding children an egg a day and daily orange juice is vital, and that the more milk a child drinks the better, although pediatricians do not encourage excessive consumption of milk. The very young children are given the same foods day after day, following directions from printed slips, and there is not much emphasis placed on varying the diet. Could it be that these procedures could be related to unexplained anorexia which is common and which may be allergic, and to really definite allergic food reactions? Apparently it is worth consideration, then, that the chief offenders are those foods which are given daily.

ALLERGY DUE TO FOOD ODORS

Dr. Arthur J. Horesh: Food odors and vapors, especially those from cooking, do contain sufficient allergenic substance to cause allergic symptoms in certain individuals. This is now an established fact, but one which has received but meager attention. Scent has a physico-chemical basis and is propagated by minute particles termed osmyls. Osmyls may act as inhalant allergens to produce allergic symptoms.

We have been especially interested in the effects of food vapors on infantile eczema. In well controlled experiments, the dermatitis of many of these infants was made worse by exposure to certain food odors or vapors. We are now convinced that sensitivity to food odors and vapors occurs very frequently in all allergic conditions and the incidence is especially high in infantile eczema. (Case reports were given demonstrating the production of allergic symptoms by food odors or vapors.)

In summary, the fact that food odors and vapors can cause allergic disturbances has the following significance:

1. It illustrates how exquisite may be the degree of sensitiveness to foods in allergic infants and children.

2. It demonstrates that in the management of the very severe cases of infantile eczema, the elimination of suspected foods from the diet alone is sometimes insufficient. Keeping the infant out of the kitchen when these foods are being prepared and away from the family table at meal time is sometimes necessary.

3. In some patients with asthma who persist in having frequent periodic attacks despite everything the physician does for them, one should keep in mind the possibility of sensitization to food odors or vapors.

4. It enlightens us on the causes of some attacks of angioneurotic edema and urticaria in patients whose food sensitivities are well known. We have noted that both parents and physicians have frequently failed to detect the cause for some of these attacks unless the possibility of symptoms being produced by food odors and vapors is kept in mind.

5. It may explain why many infants with atopic dermatitis improve dramatically in the hospital only to relapse within a day or 2 after arriving home. We previously had assigned these exacerbations predominantly to the effects of household inhalants. These undoubtedly are important but food odors and vapors are factors in many of these cases.

6. It may explain why infants may be allergic to foods which they have never eaten.

It is generally believed that the manner of sensitization to foods which the infant has never eaten is intrauterine or through the breast milk. Sensitization over these routes probably does explain most of these cases. However, we do not find it difficult to believe that infants may be sensitized to foods also in another manner, namely, by the inhalation of food odors and vapors.

FOOD ALLERGY AS RELATED TO BEHAVIOR PROBLEMS IN CHILDREN

Dr. Susan C. Dees: Behavior problems are common in allergic children. In certain patients they may represent the only clinical expression of a food allergy.

Behavior problems of childhood are of 2 principal types, first, those which are related to attitude toward food and the gastrointestinal tract itself, i.e., anorexia, capricious appetite, dawdling, gagging, refusal of food, vomiting and bowel disturbances. Secondly, those which pertain to the nervous system and include tension, overactivity, irritability, restless sleep, sleep disturbances, fatigability, temper tantrums, breath holding and overdependence. In older children the feeding problems become more complex than they are in infancy, since they are expressed physically, psychologically, vocally and altered by parental attitudes. A physiologic basis for these symptoms may rest on altered gastrointestinal motility and abnormal electric activity of the central nervous system due to food allergy.

The expression of food allergy may be the product of several factors, (1) the degree of sensitivity, (2) the number of sensitivities, (3) the frequency or timing of the ingestion of food, (4) the age of the patient.

When food allergy is proved by withdrawal and reintroduction of allergenic food one often sees behavior problems wane and wax. When one has parental cooperation, the investigation of a food allergy is a feasible procedure for any pediatrician. True, it may be a form of psychotherapy, diverting attention from the child to the food. Suggestion must enter into the management of such cases, but suggestion enters into all forms of clinical therapy. If we satisfy ourselves that we can provoke symptoms from a certain food, that we can make them disappear with its removal from the diet, and if the child shows other objective evidence of improvement in health and well being, then I believe that we are justified in using this technic in our approach to behavior problems in selected children.

TREATMENT OF POISONING BY ANTIHISTAMINIC DRUGS*

Dr. Harold I. Lecks: The treatment of poisoning by antihistaminic drugs depends upon which of the 2 types of toxic effects which these drugs may produce is elicited in the patient:

1. Convulsions; excitement; delirium—The treatment for this is ether anesthesia, by mask or administered rectally (1 oz. or 30 cc./20 lbs. or 10 kg. body weight). Paraldehyde, morphine and chloral hydrate may also be used. Barbiturates and morphine should not be employed as these are synergistic with the antihistaminic drugs as regards their toxic effects under these conditions.

2. Excessive somnolence; coma; stupor—The treatment of choice is amphetamine (benzidrene sulfate) which may be obtained in 1 cc. ampoules, each of which contains 10 mg. of the drug. This is administered in doses up to 40 mg. intravenously or intramuscularly. After the initial dose, half this amount is given every 4 hours until the patient is able to take the drug orally. Ephedrine sulfate, caffein or coramine may also be used parenterally.

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* To be published in full at a later date.

Round Table Discussion

PRESENT DAY ATTITUDES TOWARDS BREAST FEEDING

CLEMENT A. SMITH, M.D., Boston, *Chairman;* CLAUDE HEATON, M.D., New York City; JANE Y. HARSHBERGER, R.N., Boston; BENJAMIN SPOCK, M.D., Rochester, Minn.; IRA T. NATHANSON, M.D., Boston

KATHERINE BAIN, M.D., Washington, D.C.; E. R. KIMBALL, JR., Evanston, Ill., *Secretaries*

VIEWPOINT OF THE PEDIATRICIAN

Chairman Smith: In their approach to breast feeding, as to religion, pediatricians might be classified in 3 groups. There are the firm believers, with serene faith that all women ought to nurse their babies because "breast feeding is best feeding." At the other extreme, certain agnostics hold that it makes no important difference whether a baby is breast fed or given a formula. Much the most numerous are the third group, who would be glad to have a faith to stand up for if the rational basis of such a faith were revealed to them. These conscientious physicians, anxious to give sound scientific advice, find themselves falling back among traditions and impressions, in the absence of modern factual knowledge. Much new data concerns only premature infants, for whom it is quite possible that Nature did not design human milk. Obviously we need facts. Are the antibodies in human milk significant? Does it protect against neonatal diarrhea? Does suckling cause uterine involution? What constitutes optimum growth in infancy? Does it result with artificial feeding?

Without the answers to these and other questions the subject escapes into psychologic and emotional fields since it cannot be properly tackled in physiologic territory. Indeed whether a mother will nurse her baby is now usually decided psychologically rather than physiologically. If 72% of New Hampshire babies leave the maternity hospital on bottle feeding only, compared to 10% of those in South Carolina, the psychology of South Carolina women, and of their doctors, must differ from that of those in New Hampshire. And here the practising pediatrician—unless firmly convinced by present data that bottle-fed babies secure every advantage of breast-fed ones—can make his greatest contribution. Although lacking in up-to-date evidence, we certainly have no proof that bottle feeding is superior to breast feeding for American babies. Nor have we, indeed, clear proof that bottle feeding is quite as good as breast feeding. Our attitude should therefore be that while urging further research, we will not slacken in our individual and joint efforts to promote breast feeding, and to acquaint ourselves with every means for making it more successful and therefore more acceptable to the mothers of our patients.

VIEWPOINT OF THE OBSTETRICIAN

Dr. Claude Heaton: A study was made on the obstetric ward at Bellevue Hospital in an attempt to determine how mothers felt about nursing their babies. Patients were interrogated on the first day postpartum. While no coercion was used, a short talk on the advantages of breast feeding was given to primiparas who did not want to nurse. A few of these mothers changed their minds and nursed.

The figures given represent the status of nursing on the first day postpartum and on the day of discharge from the hospital. It is probable that a follow-up during the postpartum weeks would reveal a much lower percentage of breast-fed babies.

Total Patients Delivered 187	Multiparas 109		Primiparas 78	
First Day Postpartum	No.	Percentage	No.	Percentage
Want to nurse	80	73	60	77
Refuse to nurse	26	23	9	11½
*Not asked	3	4	9	11½
Total	109	100%	78	100%
Put on formula for medical indications	10	9%	9	11½
Did not want to nurse but changed minds and nursed	2	1%	2	2½

Corrected Rate

Day of Discharge Total Patients Delivered 187	Multiparas 109		Primiparas 78	
	No.	Percentage	No.	Percentage
Actually nursed	72	66	53	67
Did not nurse	34	30	16	20
*Not asked	3	4	9	13
Total	109	100%	78	100%

* Stillbirths, premature infants.

Figures were also obtained from a voluntary hospital for a few private and semiprivate cases as well as ward cases on a slightly higher economic level.

No. of Babies in Nurseries December 1947—140

	Babies	All Breast-fed	Breast and Formula	All Bottle
Private physicians	90	18 or 20%	22 or 24.4%	50 or 55.5%
Ward cases	50	23 or 46%	22 or 44%	5 or 10%
	140	41 or 29.2%	44 or 31.4%	55 or 39.2%

In conclusion, it would seem that a fairly high percentage of mothers would still like to nurse their babies. Obstetricians should encourage and help these mothers beginning early in the prenatal period and do everything possible to cooperate with pediatricians and nurses to encourage breast feeding.

VIEWPOINT OF THE OBSTETRIC NURSE

Miss Jane Y. Harshberger, R.N.: The advantages of breast feeding for the normal mother and infant are well recognized. Does the lay public perhaps prefer artificial feeding because of our highly civilized, efficient and streamlined way of life? Breast feeding may be overshadowed by formula equipment when department stores demonstrate such articles as lovely electric bottle sterilizers and hospitals have gone streamlined with expensive autoclaves and monel metal lined, clean and dirty formula rooms. Moreover women increasingly fear the tie to the home. Unless the young mother in her small apartment can go and come when she pleases, she believes she will be unhappy and lonely.

Might not breast feeding then be made as desirable as artificial feeding? Education of the expectant mother, and her husband, from early pregnancy is the answer. Teaching as to the anatomy and function of the breast and the value of nutrition should begin months ahead of delivery. The obstetric nursing supervisor is challenged to indoctrinate the nurses of the future with the belief in the value of breast feeding and a desire to advise young parents. If the nursing profession, the obstetricians, the pediatricians and the general practitioners are of one mind, then the lay public will no doubt be influenced.

If, during the first few days following delivery, the mother is taught the technics of breast care and if she and the baby learn nursing together, attitudes of satisfaction should develop. During this time, the nurse must demonstrate patience, tolerance, understanding and kindness in helping to overcome any fears or tensions. She should realize the value of helping the patient to assume the position most comfortable for her. Rocking chairs and foot stools are becoming more prevalent throughout maternity departments. The nurse should plan her time so that each new mother will have her individual attention until both the mother and the baby have become so well acquainted that each understands what the other is doing. Whatever extra time is required increases the benefits of the end result.

The fact that the mother does better if not hurried by a rigid routine is an argument for self-demand feeding. Overcrowded nurseries, shortage of nurses, and insufficient time do not always make it possible to cater to individual differences. Perhaps these are the best reasons for rooming-in, for hospital units where the mother and her baby can be together, so that she can learn how to care for and can become well acquainted with this new personality before going home.

EMOTIONAL ASPECTS

Dr. Benjamin Spock, M.D.: I assume from the start that nothing can be proved concerning the emotional factors in breast feeding but I believe that discussion may clarify the variety of psychologic issues involved.

The best evidence of the emotional value of breast feeding comes from such statements of mothers as: "It makes me feel closer to him," "It's wonderful to be giving him something that no one else can give," "It's pleasurable, physically and emotionally." Absence of physical affection has been shown to wither an infant's personality. Breast feeding affords one natural occasion, repeated a thousand times, for giving the baby this vital gratification. On the other hand, most psychiatrists would probably agree that breast feeding may be emotionally detrimental to the woman averse to it, and eventually to her child because of the effect on their relationship. A mother's deep repugnance may be disguised under a variety of excuses.

But lack of enthusiasm for nursing is not a fixed factor in the individual woman. Local custom over which physicians and nurses have some control plays an interacting part. A young woman who has casually accepted the neighborhood opinion that breast feeding is outdated may be delighted with the experience if she is encouraged to try it. At the opposite extreme, the mother versed in psychologic theory who is most tensely insistent on breast feeding may show by her uneasiness and lack of success that she is really motivated by sense of obligation rather than by maternal readiness. Other cultural factors are our educational philosophy which stresses the importance of the work of the world and neglects the satisfactions of family life, and the impact of advertising with its emphasis on youthfulness and glamor. The potent effect of both is to make even the best hearted of women feel somewhat trapped and imprisoned by child rearing. She resents it.

But these cultural and individual elements which discourage breast feeding are no more responsible, and perhaps less so, than the attitudes and procedures of the doctors and nurses. They also have not only their habits but their deep feelings too. The obstetrician who favors breast feeding detects the itch in certain pediatricians to shift to formula, and the pediatrician who strives for breast feeding is frustrated by the obstetrician who seems eager for any excuse to wean. The occasional nursery nurse, who spends some of the most crucial minutes with the inexperienced mother, may, from unconscious motives of which she has no awareness, subtly underline the mother's confidence in her ability to nurse and reduce her to tears.

In summary, then, parents, physicians and nurses, all have conscious and unconscious attitudes which interact with custom to influence the success or nonsuccess of breast feeding. Its emotional value to babies we will probably continue to judge on the basis of our individual emotional convictions.

LACTATION AND BREAST DISEASE*

Dr. Ira T. Nathanson: Various factors including postponement of pregnancy and suppression of lactation have apparently led to an increase in several benign breast lesions commonly seen today.

While cancer of the breast occurs in a high percentage of nulliparous women and adenofibrosis, a common benign lesion, arises almost exclusively in the breast of nullipara, another and increasingly frequent nonmalignant syndrome of dilated ducts, with stasis and periductal mastitis, usually follows pregnancy. Hormonal or other artificial suppression of the originally normal lactation of many such

* This is publication #715 of the Cancer Commission of Harvard University and #137 of the Pondville Hospital.

women may result in incomplete involution and pathologic changes. In other women, however, similar changes may result from endocrine abnormalities or failure to respond to a normal stimulus with proper lactation. A subsequent complete lactation in patients who can lactate normally may revert the breast to a normal state.

Initial changes in the puerperium may be engorgement of the breast with subsequent failure, hypogalactia or faulty lactation. Although judicious use of either androgens or estrogens may then alleviate the symptoms of the engorgement and permit normal lactation, the same hormones may be used to suppress lactation. Dosage levels appear to be important; thus dosages of estrogenic hormones below certain levels may actually enhance lactation, whereas higher doses may inhibit it. However, the inhibition often is not complete, the estrogens reducing lactation primarily by suppression of the lactogenic hormone, but also preventing regressive changes in the breast. When estrogens are used early in an attempt to inhibit lactation there may also be incomplete involution of the postpartum uterus and troublesome uterine bleeding. Moreover, the possible relation of estrogens to carcinoma of the breast must also be considered. Although probably fortuitous, a number of cases of carcinoma of the breast in young women have been seen within a relatively short period after receiving estrogen therapy for inhibition of lactation. The use of androgens for inhibition of lactation is open to similar criticisms, although uterine complications and the remote possibility of breast cancer are less likely. Thus, it is the opinion of the writer that future possible complications may vitiate hormonal suppression of lactation; although the same may be said for suppression in general, when inhibition is justified the older methods or androgens are preferable.

The recent discovery of a so-called mammary tumor agent in the milk of mice susceptible to breast cancer has caused considerable concern regarding a similar possibility in the human being. Evidence for such an agent (now believed to be a virus) in the human being is lacking and it appears to be unwise to recommend artificial feeding of the infant on this basis alone. This problem needs considerable investigation with long-term studies which are now in progress.

It may be concluded that lactation, as a physiologic function, should be promoted and encouraged to fruition whenever possible. Increasing evidence indicates that deviations from normal lactation, whether spontaneous or induced, may lead to breast disease.

DISCUSSION

Space considerations preclude presentation of individual questions and answers, and the imperfections of mechanical reporting have prevented introduction of the numerous participants by name. The very active discussion at both sessions of this round table followed the same general pattern. It was the majority view that whereas breast feeding had declined, there were, nevertheless, certain evidences that many more mothers wish to try nursing than succeed with it, and therefore that doctors and nurses do not give sufficient help in establishing breast feeding, from lack either of knowledge or of enthusiasm. There was strong general agreement that preparation of the mother for the experience (and for the temporary setbacks) of nursing must be begun by obstetric and pediatric cooperation at an early stage of gestation, and perhaps by education even before pregnancy. Other help can come (a) from rooming-in or from relaxation of rigid nursery rules so that infants and their mothers are brought together earlier and more often, (b) from less consideration of the infant's weight chart, with less prelacteal feeding (and no concern if gain does not begin till the second week), (c) from more frequent examination of the breasts and (d) from simple cleanliness of the nipples, nursing at both breasts at each feeding, and the prompt use of penicillin at the threat of cracks or abscesses.

Some time was spent in presenting—and sufficiently controverting—the consideration that the full time professors of pediatrics today give insufficient attention to instruction of their students in matters of infant feeding and maternal nursing. From this arose a reiterated demand for factual rather than emotional studies of human milk versus cow's milk as infant foods.

Relationship of artificial feeding to breast cancer was discussed as important but not proved in terms of quantitative correlation. Suppression of breast function may be physically harmful to the mother. Although in experimental mice cancer may be passed from one generation to another by suckling, the disturbances associated with suppression of lactation in the human mother are considered a much greater danger.

In summary, it was felt that at least 50% of women wish to nurse their infants for the first 3 months. Most of them could do so if properly prepared intellectually and physically during pregnancy, and allowed hospital routines providing flexibility, time and cooperation in starting the actual process.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

COMMUNICATION FROM DR. FRANZ GOLDMANN

PAYMENT FOR PHYSICIANS' SERVICES UNDER CRIPPLED CHILDREN'S PROGRAMS

ADEQUATE remuneration of the participating members of the health professions is one of the prerequisites for the effective operation of medical care programs and, especially, for the maintenance of high standards of service. There can be no doubt about the importance of this subject to the individual physicians expecting a compensation commensurate with the value of their services, to the public or voluntary agencies charged with administrative responsibility for medical care programs, and to the voluntary organizations directly or indirectly concerned. Yet, surprisingly few studies have been made on the methods and rates of payment to those physicians and members of other health professions who render service under the various types of medical care programs recently developed, and only feeble efforts have been made to evaluate the various methods, with special emphasis on the adequacy of payment to the professional persons, the effect on the quality of service, and the administrative implications.

The Crippled Children's Programs lend themselves particularly to an investigation of their payment policies, because of their long record of operation, their important place among the programs of public medical care, and their substantial annual expenses for the services of physicians and dentists. In order to obtain information on their practices in compensating the participating members of the medical and dental professions in private practice a special study was undertaken in 1948 at the request of the National Foundation for Infantile Paralysis and the Federal Security Agency, Social Security Administration, Children's Bureau. The major part of the material for the analysis was gathered from the voluminous files in the Division of Health Services, Children's Bureau, containing the reports of all the administrative agencies in the states and other jurisdictions on both the

current programs and the basic five year plans contemplated. Supplementary data and clarification of doubtful statements were obtained through correspondence or conferences with the executive officers of state agencies.

The material collected, although not suitable for conclusions on many points of general interest, nevertheless was sufficient for the purpose of determining the broad policies that have evolved out of many "trial and error" efforts in the early years of the programs.

The findings are described in detail in a report submitted to the National Foundation for Infantile Paralysis and the Division of Health Services, Children's Bureau.* As was to be expected, diversity rather than uniformity is characteristic of the policies. The degree of variation, however, is rather surprising. The methods and rates of payment to the participating physicians and dentists in private practice differ considerably not only from agency to agency but, within the jurisdiction of the same agency, from one type of program to the other, namely, the programs for children with orthopedic conditions, the rheumatic fever programs, the cerebral palsy programs, the services for children with impaired vision, and the services for children with impaired hearing.

In the majority of all states three methods of payment, the fee-for-service method, the flat rate method, or the part-time salary method, are employed to compensate physicians for the same type of professional service, such as attendance at diagnostic clinics, consultations outside of clinics, or treatment. In some instances, no arrangements for payment have been made; the administrative agencies accept services donated by physicians in private practice or utilize the services of physicians employed by public hospitals.

At first glance the picture seems to be like a mosaic without any design. Closer study, however, reveals that there are definite patterns, and these will be described in the following sections.

Terminology

The terminology used by the reporting state agencies was anything but uniform and quite frequently was not only at variance with scientific usage but too vague to permit correct interpretation. In order to avoid confusion all statements appearing in the official reports were examined and grouped according to the following system of classification:

1. Fee-for-service method: a system under which participating physicians and dentists receive specified fees according to the type and number of services actually rendered

Fee schedules: a system under which the maximum fees are defined in special schedules formulated by the administrative agencies in cooperation with representatives of the professions concerned

2. Flat rate method: a system under which the participating physicians and dentists receive fixed amounts of money in proportion to the total amount of work for all patients

Flat rate per unit of time: a system of paying a fixed amount per hour, half day, or full day actually worked, regardless of the number of patients seen

Flat rate per clinic session: a system of paying a fixed amount for each clinic session actually held, regardless of the number of hours worked or patients seen

3. Part-time salary method: a system of paying monthly or annual rates of compensation for performance of certain duties, regardless of the number of patients actually seen or the number of services actually rendered.

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* Franz Goldmann, *Payment for Physicians' Services under Crippled Children's Programs.* Reproduced by Federal Security Agency, Social Security Administration, Children's Bureau.

Payment for Service at Diagnostic Clinics

The clinic services are limited to diagnostic work and follow-up in the great majority of all states, are extended to treatment of minor conditions in a small number of states, and include treatment of ambulatory patients as well as diagnostic service and follow-up in a few instances. Both "field clinics" ("itinerant clinics") and permanent clinics are maintained. All types of clinics were considered in studying the compensation of physicians.

Payment to the physicians conducting clinics is made most frequently by allowing flat rates, either per unit of time or per clinic session, somewhat less frequently by using the part-time salary system, and only rarely on the basis of the fee-for-service system. The majority of all agencies employ two methods for different types of programs, a slightly smaller proportion employ one method for all their programs, and a few follow three different policies for various types of programs.

Where a single method is employed, payment on the basis of flat rates per unit of time, e.g., per half day or full day, is most common, closely followed by payment of part-time salaries. Of the agencies employing two methods, the majority give preference to the payment of flat rates per clinic session and the payment of part-time salaries; they use these systems either in combination for the same type of specialist or side by side, each applied to the compensation of specified groups of specialists. A smaller number allow flat rates per unit of time and part-time salaries, and some follow various other practices.

The flat rates per time spent on conducting field clinics in 1948 usually amounted to $25 for a half day and ranged from $25 to $75 for a full day, the amount of $50 being most common. In general, the compensation for attendance at field clinics was higher than that for work at local clinics. In some states diplomates of a specialty board or physicians eligible for certification received more than was allowed for physicians without a specialist diploma or equivalent professional training and experience. In others, the rates of compensation differed substantially according to the type of program, e.g., orthopedic program, rheumatic fever program, or hearing conservation program, and in still others differentiation was based on the type of specialist, orthopedists ranking higher in the pay scale than pediatricians.

The part-time salaries usually cover several types of service, such as attendance at diagnostic clinics, certain treatment services, and consultations outside of clinics. Typical salary scales will be described in the sections on compensation of pediatricians and of orthopedic surgeons.

Payment for Consultation Outside of Clinics

Many agencies include in their programs individual consultations in the home of the patient, the office of the physician, and the hospital, although with variations in both the scope of provisions and the administrative controls. Some programs exclude either home visits or office visits while others adhere to no definite practice. In general, consultations are made available with or without special authorization upon request of physicians anxious to establish the correct diagnosis or review the treatment plan. Some agencies allow "formal consultations" by specialists only after the failure of previous efforts to arrive at a definite diagnosis. Not infrequently individual consultations are arranged by the administrative agencies for those children who for one reason or another cannot be seen at the scheduled clinic sessions. The general tendency seems to be to place the emphasis on utilization of

the regular clinic sessions and to supplement this service by provisions for individual consultations outside of clinics under special conditions only.

In analyzing the file material efforts were made to eliminate statements obviously referring to routine home or office visits and to single out formal consultations for the purposes of clarifying the diagnosis, determining the treatment plan, or reviewing the case. In a number of instances this approach proved to be futile owing to the rather loose application of the term consultation. Reports from 43 agencies were found to contain information sufficient to warrant broad conclusions.

Of 43 agencies, 15 employed one method of paying for consultations outside of clinics, 24 employed two methods, contingent on the type of program or type of specialist, and four employed three methods. The predominant policies were payment of specified fees and inclusion of consultations in the services covered by part-time salaries.

The fees paid for consultations in 1948 varied greatly, depending not only on the region of the country and the type of specialty but also on the content of the consultation. According to the data available the amount of $10, covering examination, report and recommendation, was the prevailing fee for most types of consultations, and higher rates were not uncommon for psychiatric and neurologic consultations or complete examinations of children with congenital heart disease. In many instances additional fees were paid for second visits necessary to complete the examination by the consultant, and occasionally ceilings were placed on the total amount of compensation allowed per month. As to part-time salaries reference is made to the sections on compensation of pediatricians and of orthopedic surgeons.

Payment for Treatment by Physicians

Treatment of children accepted in accordance with the eligibility requirements is a dominant feature of the Crippled Children's Programs in all states. The provisions for treatment include service in the home, office, and hospital in a number of states and exclude home visits, office visits, or both in some states.

All the states and the District of Columbia have made definite arrangements for the compensation of general physicians as well as specialists rendering treatment services, but their policies in regard to the methods and rates of payment are dissimilar in many respects. However, it is significant that payment for treatment by physicians, both specialists and general physicians, is made most frequently on the basis of the fee-for-service system and less frequently on the basis of the part-time salary system.

Of the 49 agencies studied, 14 employed one method of payment, 27 employed two methods for different specialists or the various types of programs, and eight employed three methods. The fee-for-service system was utilized by 38 agencies, as the only method in eight instances and together with a variety of other methods in 30 instances. Part-time salaries were paid by 28 agencies, three using this system exclusively and probably as many as 25 using it in combination with other methods, although verification was possible in 16 instances only.

Of the 14 agencies employing one method only, eight paid on the basis of the fee-for-service system, three on the basis of the part-time salary system, two utilized the services of physicians without compensation, and one allowed flat rates. In the group of 27 agencies employing two methods there were certainly 11 and probably 19 which paid fees to some physicians and part-time salaries to others, three which used the fee-for-service system

and also relied on donated service, and five with various combinations of methods. The eight agencies employing three methods used a large variety of combinations.

In most states the fees allowed for certain services are set forth in special schedules. In some instances these lists are the result of negotiations with the organizations representing the physicians, in others they are drawn up by administrative agencies to serve merely as unofficial guides. In a few states the fee schedules for recipients of public assistance are utilized.

To control the cost under this system, some agencies require initial authorization for all services or for services costing more than a stated amount, others set upper limits for the amounts of compensation per case or per period of time, and still others pay inclusive rates for all services rendered to a patient in connection with an operation or during a certain period of time.

Table 1 shows the various methods of paying for specified types of service in their order of frequency.

TABLE 1

METHODS OF PAYING FOR SPECIFIED TYPES OF SERVICE, BY FREQUENCY

Payment method	Service at diagnostic clinics	Consultation outside of clinics	Treatment by physicians
Fee-for-Service	3rd	1st	1st
Flat Rate	1st	3rd	3rd
Part-time Salary	2nd	2nd	2nd

PAYMENT FOR SERVICES BY DENTISTS

At least one half of all agencies responsible for Crippled Children's Programs make provisions for dental care, some following a very liberal policy and some keeping this service within narrow limits. Information from 22 agencies indicates that orthodontia as well as roentgenographic examinations, fillings, and extractions are made available by a considerable number of agencies.

With the exception of two states which utilize their full-time salaried dentists, all the agencies pay for general dental services on the basis of the fee-for-service system. Often the fees are specified in schedules, and occasionally the total amount allowed per case of general dentistry is limited.

In paying for orthodontic service the majority of all states employ the fee-for-service method; the minority allow flat rates, pay part-time salaries with or without additional fees for specified services, or relate the compensation to the number of hours worked. Several agencies place a ceiling on the total amount of money allowed per case of orthodontia or per year of treatment, and one agency obtains orthodontic services at a 50% discount from the ordinary fees.

COMPENSATION OF PEDIATRICIANS

In compensating pediatricians the majority of the agencies use the fee-for-service

system, a substantial number employ the flat rate method, and many make use of the part-time salary system. There seems to be no definite policy in employing these methods for the purpose of paying for the three major types of professional service rendered by pediatricians. Multiplicity of practices is the rule, and the combinations of various payment methods are numerous.

The policies governing the compensation of pediatricians differ markedly from those adopted for the remuneration of orthopedic surgeons. The fee-for-service system ranks first in order of frequency with regard to pediatricians and second with respect to orthopedic surgeons. The flat rate method occupies the second place in the organization of payment for the services of pediatricians but is the prevailing method of compensating orthopedic surgeons. The part-time salary system comes third for both groups. Only one state includes the compensation for all three types of professional service in the part-time salaries of pediatricians, in contrast to at least seven and probably a much larger number of states adhering to such a policy in the case of orthopedic surgeons.

A few examples will serve to illustrate the multiformity of policies.

1. Fees in combination with flat rates.

In Oregon, in 1948, flat rates ranging from $50 for one day to $175 for three days were paid for attendance at diagnostic clinics and a fee of $7.50 was allowed for a consultation (initial examination) outside the clinic, a fee of $3.00 was paid for a follow-up examination or visit, with a maximum of four visits per week and $50 per month for continued care, and a flat rate of $10.00 per case was allowed for preoperative and postoperative pediatric care of "routine uncomplicated cases."

In Texas, in 1948, a flat rate of $50 per day was paid for service at diagnostic clinics and a fee of $10 for a consultation (initial examination) outside the clinic; specified fees were allowed for treatment, with a maximum of $15 for the first week and $12 for each subsequent week up to a maximum of $100 for any one patient.

2. Fees in combination with part-time salaries and flat rates.

In Idaho, in 1948, part-time salaries of $1,800 were paid for attendance at diagnostic clinics, supplemented by flat rates of $30 or $60 per half day or full day, respectively, for clinics held outside Boise, and a fee of $15 was allowed for a consultation (initial examination) outside the clinic; specified fees were paid for treatment, with a maximum of $45 for the first four weeks and of $9 per week thereafter.

3. Part-time salaries.

In Kentucky, in 1948, the pediatricians received part-time salaries, ranging from $150 to $600 a year, in payment for all three types of professional service except home visits. Some of the pediatricians worked two or three months each on a rotating basis.

4. Part-time salaries under one program and part-time salaries in combination with fees under another program.

In South Carolina, in 1948, the pediatricians rendering service under the rheumatic fever program received part-time salaries, ranging from $600 to $1,800, for attendance at diagnostic clinics, consultations outside of clinics, and treatment. On the other hand, those participating in the orthopedic program received part-time salaries covering clinic sessions and consultations outside of clinics and, in addition, were paid fees for treatment, amounting to $5.00 for the first visit and $3.00 each for four subsequent visits up to a total of $17.00 and limited to a total of $40.00 for continued care, including intercurrent illness.

Compensation of Orthopedic Surgeons

The compensation of orthopedic surgeons is based on the flat rate system, the fee-for-service system, or the part-time salary system in this order of frequency. The employment of these methods in paying for the three basic types of professional service—attendance at diagnostic clinics, consultation outside the clinic, and treatment—varies greatly from state to state, and different policies for different programs or specified types of professional service are quite common.

In at least seven states the orthopedic surgeons receive part-time salaries for attendance at diagnostic clinics, individual consultations outside of clinics, and treatment, including operative procedures and postoperative care, the amounts ranging from $600 to $4,200 a year, and in at least 11 additional states the part-time salaries cover diagnostic clinic service and treatment. In some instances the basic remuneration through payment of part-time salaries is supplemented by flat rates for clinic sessions in distant areas or by fees for emergency calls. Combination of flat rates for clinic service with fees for consultations and treatment is another widely used policy.

The following examples will serve to show details of the principal policies.

1. Flat rates in combination with fees.

In California, in 1948, flat rates of $25 and $50 were paid for a half day or a full day, respectively, of service at a diagnostic clinic, a fee of $10 was allowed for a consultation (first examination) outside the clinic, and specified fees were paid for treatment including two weeks of postoperative care, with a flat rate of $6.00 per week, or $24 a month, for hospital visits after the first two weeks and a maximum of $300 for any one case.

In New York, in 1948, service at diagnostic clinics was compensated at the rate of $25 per clinic session plus $7 per hour after the first three hours up to a maximum of $50, a fee of $10 was paid for a consultation (first examination) outside the clinic, and specified fees were paid for treatment including surgical after-care, with a maximum of $80 per year for supervision and treatment of hospitalized patients requiring no surgery and of $60 per year after expiration of surgical after-care.

In Missouri, in 1948, a flat rate of $50 was paid for a clinic session and a fee of $5.00 for a consultation outside the clinic. Flat rates were allowed for treatment of inpatients, the annual maximum being $125 for patients in hospitals and convalescent homes ($50 for the first quarter and $25 for each additional quarter), and a fee of $3.00 was paid for each outpatient visit.

2. Part-time salaries.

In Alabama, in 1948, part-time salaries ranging from $2,800 to $3,800 per year covered service at diagnostic clinics, consultations outside of clinics, and treatment including operative procedures and preoperative and postoperative care at the hospital and office.

3. Part-time salaries in combination with fees.

In Massachusetts, in 1948, part-time salaries of $975 per year covered service at diagnostic clinics and treatment including operative and postoperative care, fees were paid for consultations outside of clinics, and occasional extra payments of $5.00 per patient were allowed, with a maximum of $75 for an additional clinic session.

4. Part-time salaries in combination with flat rates.

In West Virginia, in 1948, part-time salaries ranging from $3,000 to $4,200 covered service at diagnostic clinics, consultations outside of clinics, and treatment including pre-

operative and postoperative care at the clinic, hospital, and office. Two orthopedic surgeons received an additional payment of $100 per quarterly clinic session.

Comparison of Fees

Table 2 presents the payment methods for the services of pediatricians and orthopedic surgeons in their order of frequency.

In many states there are marked differences in the fees allowed for the same type of service. A sample study of five states showed for instance that the fees for the operation of a congenital clubfoot ranged from $50 to $150 and those for the primary closure of a cleft palate from $70 to $150.

TABLE 2

Methods of Paying for Services of Pediatricians and Orthopedic Surgeons, by Frequency

Payment method	Pediatricians	Orthopedic surgeons
Fee-for-Service	1st	2nd
Flat Rate	2nd	1st
Part-time Salary	3rd	3rd

The reasons for this disparity in paying for the same type of service requiring the same skill and time cannot be stated due to lack of pertinent information. Whether the fees actually paid for the various surgical and orthopedic procedures constitute a fair compensation is a question that cannot be answered without knowledge of the basis used for the determination of fees. There may have been bargaining between the agency stating "this is what we shall pay" and the physicians maintaining "this is what you must pay if we are to work for you." There may have been an earnest effort to develop an equitable fee schedule on an objective basis, or there may have been a tendency to regard participation in the program as another form of "charity service" to be paid for at "charity rates."

Tempting, indeed, is the idea of comparing the fees for identical services under different types of official programs of medical care, such as the Crippled Children's Programs, the Vocational Rehabilitation Service, Workmen's Compensation, and the medical care provisions of the Veterans' Administration. However, it should be borne in mind that certain surgical operations, such as those for congenital deformations, are quite frequently performed under Crippled Children's Programs and the Vocational Rehabilitation Service but not at all under Workmen's Compensation or the program of the Veterans' Administration. On the other hand, certain services, such as treatment of fractures, are very common under Workmen's Compensation or the program of the Veterans' Administration but rare under the other two programs. Apart from these considerations comparison of fees under various medical care programs poses intricate problems. Some agencies include specified, and often varying, periods of after-care in the fees for surgical operations, and others pay additional fees for all subsequent service or services after a specified period. Some agencies allow specified fees for either reductions or plaster casts plus cost of materials, and others pay inclusive rates for the surgical procedure or for the plaster cast and manipulations. The variations in policy are legion, and little can be gained from comparative studies unless all the facts are known.

Only very broad conclusions can be drawn from the material available for this study. In some states, such as California and New York, the Crippled Children's Programs, the Vocational Rehabilitation Services, and the agencies administering Workmen's Compensation pay about the same fees for the same type of service. There is reason to assume that this policy rests on agreements between the agencies concerned, especially the departments of health in charge of the Crippled Children's Programs and the departments of education administering the Vocational Rehabilitation Service. In other states, such as Kansas, the agencies administering the Crippled Children's Programs pay fees considerably below those allowed by the Workmen's Compensation agencies and the Veterans' Administration. In some states determined efforts have been made to avoid too wide a spread between the maximum fees for identical services to be paid by various official agencies, and in a few states a considerable degree of uniformity has been achieved. In Michigan, a "Uniform Fee Schedule for Governmental Agencies" has been adopted.

Reimbursement of Travel Expenses

Information from 35 agencies indicates wide acceptance of the principle of reimbursing physicians for the expenses of travel in connection with both service at diagnostic field clinics and consultations outside of clinics.

Reimbursement is made by allowing specified expense items or paying flat rates per day. The reimbursable expense items include some or all of the following: fare (train, bus) or mileage if the physician uses his own automobile, bridge or highway tolls, hotels, and meals. In a few instances allowances are paid for auxiliary personnel, such as secretarial help, accompanying the physician.

A number of agencies assume responsibility for the expenses "actually incurred" or for "necessary expenses" without setting definite limits, others allow a fixed amount per day ("subsistence") in addition to the cost of transportation, still others limit the amounts of reimbursement for meals, hotel or both, and a few include travel expenses in the compensation for clinic service.

The daily maintenance rates paid in 1947 ranged from $5.00 to $7.50, and the amount of reimbursement for use of physician-owned automobiles ranged from 4.5 cents to 7.5 cents per mile, the majority of the agencies allowing 5 cents per mile.

Summary

1. Payment for the services of physicians conducting diagnostic clinics is made most frequently by allowing flat rates, either per unit of time or per clinic session, somewhat less frequently by using the part-time salary system, and only rarely on the basis of the fee-for-service system.

2. Payment for specialist consultations outside of clinics is based on the fee-for-service system and the part-time salary system in this order of frequency.

3. Payment for treatment by physicians, both specialists and general physicians, is made most frequently on the basis of the fee-for-service system and less frequently on the basis of the part-time salary system.

4. In at least eight states, the part-time salaries paid to the physicians cover a varying combination of the following types of professional service: diagnostic clinic sessions, consultations outside of clinics, and treatment, including preoperative and postoperative care as well as operative procedures.

5. Dentists, including orthodontists, are compensated on the basis of the fee-for-service system in the great majority of all states.

6. Pediatricians receive fees most frequently and flat rates or part-time salaries less frequently. Orthopedic surgeons are paid on the basis of the flat rate system, the fee-for-service system, or the part-time salary system in this order of frequency.

7. Reimbursement of travel expenses incurred in connection with both service at diagnostic field clinics and consultations outside of clinics is a widely accepted principle.

8. There is little, if any, information on such questions as the reasons for the choice of certain methods of payment, the basis for the determination of specific rates of compensation, the number of diagnostic clinic sessions actually held per month or year, the average number of hours, excluding travel time, actually spent on one clinic session, the amount of work and time actually contributed by the physicians receiving part-time salaries, or the type and amount of service rendered by physicians compensated on the basis of the fee-for-service system. In the absence of such information no conclusions can be drawn on the relative merits of the various payment methods employed and especially on the adequacy of the compensation received by the participating physicians and dentists, the effect on the quality of service, and the administrative implications.

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TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

WHO REPORTS FIRST RESULTS OF MASS VACCINATION WITH BCG

(Continued from the September issue of PEDIATRICS*)*

LOCAL REACTION IN BCG VACCINATION

IN HEALTHY individuals, vaccination with BCG produces a local reaction at the site of inoculation which appears after a period of three to four weeks, or longer, i.e., at about the same time as the first signs of allergy can be detected. Enlarged glands in the corresponding area may also be observed. This "normal BCG-itis" is often scarcely noticeable to the individual. Nevertheless, the reaction to vaccination has not always this benign character. Strong local reactions may occur. These appear in the form of an induration of 10 mm. or more accompanied, in certain cases, by ulceration, pustules, and glandular complications. The intensity of the reaction depends, among other things, on the number of bacilli (killed or living) which have been injected, on the vaccination technique, and on individual factors. Observations made by the Joint Enterprise revealed, among 14,000 persons examined 6 to 10 weeks after vaccination, 3% reactions measuring 10 mm. or more. Ulcers appear relatively earlier, i.e., between the 4th and 8th weeks; in some groups ulcers were obseıved in 0.23% of the individuals. "Local abscesses" are mentioned in some studies. Cases of glandular complications with suppuration are of the greatest practical importance. As many as 196 cases out of 62,200 individuals (0.03%) have been observed in certain countries; the left axilla was affected in most of the cases.

"If suppurating lymphadenitis, abscess formation at the site of vaccination, and local ulcers with diameters of 10 mm. or more are regarded as "complications," the proportion of these phenomena observed in the Joint Enterprise campaigns is between 0.1% and 0.5%.

"A special case of strong reaction is the "Koch phenomenon" or accelerated formation of the tuberculous nodule. It occurs much earlier than a normal reaction and appears in the form of erythema, pustules, and, sometimes, ulcers or necroses, aand may be complicated by glandular reactions. It is the result of a reinfection and appears in individuals who, before vaccination, were already infected with tubercle bacilli. This phenomenon, which was described by Koch in his experiments on animals, has been observed particularly during experiments on the treatment of tuberculosis with BCG and, in isolated cases, after BCG vaccination.

"A curious case appears in the literature on the subject:

"A girl was vaccinated with BCG on a negative Mantoux 100 TU. The post-vaccination test carried out three months later was positive. Three months after this last test she fell and injured her elbow; the lesion was accidently contaminated by sputum containing tubercle bacilli of the human type. The girl soon showed a tuberculous ulcer, and caseous

lymphadenitis became apparent in the regional glands on the 27th day after inoculation.

"Owing to the imperfections of tuberculin-tests and despite all the precautions adopted, it is impossible, during vaccination campaigns involving millions of individuals, entirely to avoid vaccinating persons infected with tubercle bacilli. The lowered tuberculin sensitivity of individuals suffering from various other diseases may result in individuals who are really infected being recorded as non-infected. For this reason, and also owing to certain individual sensitivity factors, Koch phenomena are liable to occur during mass vaccinations. The difficulty of defining the Koch phenomena exactly is one of the reasons why the statistical results on this subject are not very accurate. Nevertheless, it would appear from the various investigations that strongly marked Koch phenomena likely to prove disagreeable for vaccinated individuals are of extremely rare occurrence. Only 7 cases of ulceration were noted in a district where the percentage of tuberculin-reactors is very low. The studies carried out show that strong local reactions during the first week after vaccination seem to have occurred only very rarely in individuals who were vaccinated after giving a negative reaction to a patch-test, Mantoux 10 TU and 50 TU and an AP test. This may be taken as an indirect proof of the fact that the technique adopted for the tuberculin-testing was fairly satisfactory, as far as selection of individuals for vaccination was concerned."

Tuberculous Disease in BCG-Vaccinated Individuals

"Can BCG produce, activate, or aggravate a tuberculous infection? The question has not been definitely settled. The problem has too often been approached on non-scientific lines and should be reinvestigated with complete impartiality.

"BCG has often been accused of causing tuberculous infection, reviving latent infection, or accelerating the crisis in active tuberculosis. Before discussing the question itself, Dr. Ustvedt points out some of the misconceptions on the part of the public and the misunderstandings which are liable to occur during mass-vaccination campaigns; for example, a tuberculin test may be mistaken for a BCG vaccination; vaccination against smallpox or diphtheria may be confused with BCG vaccination; a non-tuberculous disease or normal BCG-itis may be diagnosed as tuberculosis, etc. It is certainly easy to rectify statements resulting from such mistakes and to dispose of unfounded judgments. That being done, some cases in which BCG might have played a part in the development of a tuberculous infection should be objectively examined.

"Cases of tuberculosis have occurred in individuals vaccinated with BCG. The immunity conferred by the vaccine is admittedly not absolute. Can BCG, however, be held responsible for the infection? Thorough investigation has shown that, since 1930, BCG has not caused progressive tuberculosis in laboratory animals, that it has not been virulent in human beings, and that no fact has come to light which has caused the innocuousness of this vaccine to be questioned.

"Individuals who are already infected with virulent bacilli but who did not react to the tuberculin test may be vaccinated. It was stated earlier that these tests do not reveal all the infected persons. Cutaneous sensitivity may be greatly reduced in individuals who have previously suffered from tuberculosis and may decline or disappear during infectious diseases such as pertussis or measles. Moreover, the person may, at the time of vaccination, be in the pre-allergic phase of an infection caused by virulent tubercle bacilli and may not react to the tuberculin. The vaccination of such individuals—infected but non-reactors—

may cause accidents and Koch phenomena which, if violent, are likely to influence the course of the infection.

"In the Joint Enterprise campaigns, various individuals have been observed in whom the following symptoms appeared 10 to 12 weeks after vaccination: erythema nodosum, hilar adenitis, primary complex, and pleurisy. It is known that erythema nodosum may be provoked by various agents (for example, drugs and vaccines), and BCG may possibly have a similar effect. In a few cases of primary tuberculosis which occurred soon after vaccination no causal relation could be established between the vaccination and the disease. To avoid controversy, however, persons who have suffered from tuberculosis should not be vaccinated, even if they have become negative to tuberculin. The same precaution should be taken when an epidemic of a childish complaint, which weakens the sensitivity to tuberculin, has broken out in an area.

"The influence of BCG on active tuberculosis has already been the subject of much investigation. While some doctors felt that it had a certain beneficial effect, others considered that it might not always be harmless for patients suffering from active tuberculosis. When large doses of BCG are used, it must obviously be expected that such persons will show a reaction similar to that produced by tuberculin. After inoculation with strong doses of BCG, a focal reaction, a rise in temperature, the transient aggravation of pleurisy, and articular phenomena have been observed. While it cannot be said with certainty that these manifestations are a consequence of vaccination, the possibility cannot be denied absolutely. Some doubtful cases, in which it is not possible to determine precisely what part was played by BCG in the development of a non-apparent disease which sometimes proved fatal, are discussed in detail in the article by Dr. Ustvedt. This author concludes by emphasizing that, in spite of the abundant documentary evidence asserting the harmlessness of BCG, vaccination of persons suffering from active tuberculosis should, as far as possible, be avoided. Improving the tuberculin tests, thus making it possible to discriminate with increasing precision between infected and non-infected individuals, will be the surest means of attaining this end.

"In the last part of this article, Dr. Ustvedt reviews the various forms of tuberculosis observed in individuals vaccinated with BCG. Tuberculous meningitis and military tuberculosis have been observed in 21 children during the campaigns in various countries; in most cases the date of appearance of the symptoms makes it likely that the vaccination was carried out during the pre-allergic phase. There is no evidence to show that BCG vaccination contributed to the development of the disease.

"In his paper, the author points out that the isolation of human-type bacilli from a tuberculous individual is not in itself sufficient proof that BCG was not responsible for the disease. If BCG were to become virulent, it might possible present some of the characteristics of human-type bacilli, especially with regard to its pathogenicity for certain experimental animals. Cases of erythema nodosum are very controversial since they can be of non-tuberculous origin. Cases of primary tuberculosis have been observed in persons infected with virulent bacilli shortly before or after BCG vaccination. However, when the first 6 to 8 weeks after vaccination have elapsed without any superinfection and when post-vaccination allergy has been obtained, the manifestations of primary tuberculosis disappear in a striking manner. This last phenomenon is characteristic and has been observed in most of the groups vaccinated with BCG."

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

TREND IN INFANT MORTALITY RATES

CONTINUOUS decline in infant mortality has been maintained in national figures since 1936. Prior to this the preceding 20 years had witnessed a steady downward trend although there had been occasional annual interruptions. Final figures for 1948, issued by The National Office of Vital Statistics in Special Reports, Vol. 35, Number 13, p. 188, August 23, 1950, indicate a total of 113,169 deaths under 1 year of age as having

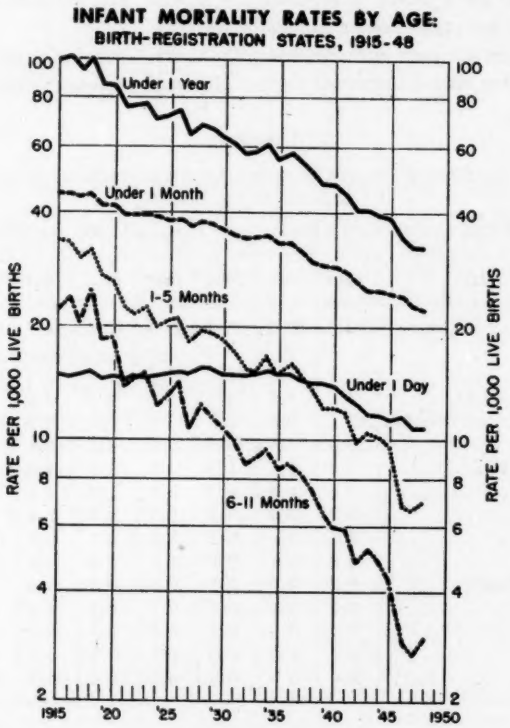

CHART 1

been registered in the United States. This represents a rate of 32.0 per 1,000 live births, the lowest in our history.

Chart 1 indicates the trend in the "Expanding Birth Registration Area" since 1915. In that year the "Area" was set up with 10 states and the District of Columbia. In 1933, with the admission of Texas, the "Area" included all 48 states. Over the 33 year period the decline in total infant mortality has been more than two thirds. The different periods of

the first year of life have not, however, shared equally in the decline. The second half of the year has had the most favorable experience with a decline of 85%, while the first day has had the least decline, less than one third. Furthermore, the entire reduction in the first day has been observed since 1935, at which time more emphasis was placed in both Federal and State public health programs on prenatal, natal and neonatal problems.

In 1915 deaths in the first month constituted less than half those in the first year; it was not until 1921 that the situation was reversed and deaths in the remainder of the first year dropped to less than half the total. Further persistent decrease reached the point where in 1946, deaths in the 11 months from the end of the first month to the end of the first year were fewer than deaths in the first day of life. The different rates of decline are related to the relative ease with which the particular medical problems can be approached. While advances in medical therapy have played an important part, perhaps even more striking has been the increased attention to well child supervision and preventive pediatrics, carried out under private and public aegis.

Progress has also not been uniform among the various causes of death. Table 1 presents data since 1915 for certain important causes. The most striking change has been in diar-

TABLE 1

INFANT MORTALITY RATES FOR SPECIFIED CAUSES: BIRTH-REGISTRATION STATES, SELECTED YEARS, 1920–48

(Exclusive of stillbirths. Deaths under 1 year per 1,000 live births)

Cause of death	1948	1947	1946	1945	1940	1935	1930	1925	1920
All causes	32.0	32.2	33.8	38.3	47.0	55.7	64.6	71.7	85.8
Premature birth	11.1	11.1	12.1	11.6	13.7	15.4	16.7	17.2	19.4
Congenital malformations	4.5	4.6	4.5	5.0	4.7	4.8	5.3	6.2	6.2
Pneumonia (all forms) and influenza	3.7	3.6	3.8	5.3	7.4	9.2	10.2	11.2	13.8
Injury at birth	3.4	3.5	3.6	3.6	4.5	4.5	4.8	4.9	3.7
Diarrhea, enteritis, etc.	1.8	1.5	1.7	3.0	3.5	4.9	7.8	11.2	14.9
Congenital debility	0.5	0.5	0.5	0.8	1.2	2.1	2.5	3.5	4.8
Whooping cough	0.2	0.4	0.3	0.5	0.9	1.4	1.5	1.8	3.0
Syphilis	0.1	0.1	0.2	0.3	0.5	0.7	0.8	0.7	0.9
Dysentery	0.2	0.1	0.1	0.3	0.4	0.4	0.4	0.3	0.4
Tuberculosis (all forms)	0.1	0.1	0.1	0.2	0.2	0.3	0.5	0.7	1.0
Convulsions	0.1	0.1	0.1	0.1	0.2	0.3	0.4	0.7	1.0
Measles	0.1	0.0	0.1	0.0	0.1	0.4	0.4	0.3	1.0
Diphtheria	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.3	0.5
Scarlet fever	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1

rhea and enteritis with a decline of 88%. From its status as the second most important cause of death in the first year, and most important after the first month, it has dropped to fifth, still more frequent than it should be. Decline in pneumonia and influenza has also been outstanding, 73%. Premature birth has shown a substantial diminution, 43%, more impressive since 1935, and even congenital malformations, once considered part of the irreducible minimum have dropped more than 25%.

Another example of existing inequality is shown in chart 2, illustrating the consistent difference between the improvement in mortality among the nonwhite races as compared

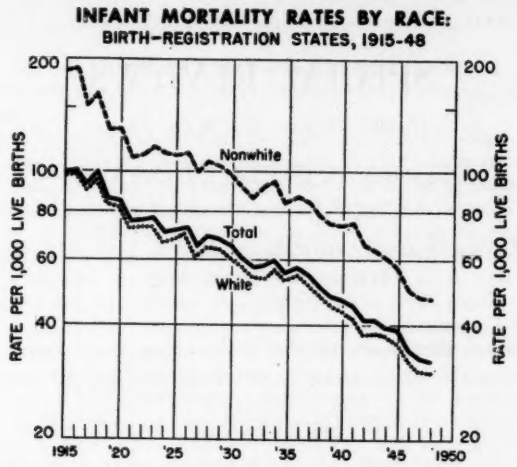

CHART 2

with the white. In general, infant mortality for the communicable diseases is much higher among nonwhite than white infants, while smaller differences between race groups appear for causes related to prenatal conditions and perinatal conditions. In 1948 the rate of pneumonia and influenza was 2½ times as high for nonwhite (7.6) as for white (3.1) infants; for diarrhea and enteritis, the rate for nonwhite infants was 2.6 and for white infants, 1.7. The death rate for accidental causes is also higher among the nonwhite infants, 1.8 in this group, and 0.9 for whites.

The advances cited are source for considerable satisfaction yet it is obvious that much remains to be done. Further improvement in regard to specific causes is entirely feasible, while there is much need for consolidating and making more uniform the gains which have already been achieved.

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

DUODENAL ULCER IN INFANCY
With Presentation of a Case

By MILTON H. HOLLANDER, *Major, Medical Corps, U.S.A.*, AND
MERITT W. STARK, M.D.,
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A case of duodenal ulcer in an infant 9 weeks of age is presented. A review of the literature has been made with bearing on incidence, etiology, pathology, diagnosis and treatment.

REPORT OF CASE

History: A white male infant, aged 6 wk., was first admitted to Fitzsimons General Hospital with chief complaint of vomiting. Patient had been a full term, normal delivery with birth weight of 2,977 gm. He was bottle fed from birth and vitamins in adequate amount had been started at 4 wk. of age.

The mother and father were living and well. The father gave a history of recurrent episodes of epigastric discomfort coming on at times of emotional stress and strain, but with no evidence of ulcer on gastrointestinal series. There were no siblings.

The infant did well until about the 14th day of life at which time he began to have occasional episodes of vomiting. These gradually became more frequent and projectile in character. This condition was helped only temporarily by atropine, elixir of phenobarbital and heavy feedings with cereal. He began to lose weight and was hospitalized. Weight on admission was 3,544 gm.

Physical examination revealed peristaltic waves over the epigastrium passing from left to right. A small mass approximately 1 x 1.5 cm. was palpable deep in the epigastrium to the right of the midline. A barium swallow the day following admission revealed no abnormality of the stomach wall. A small amount of barium was seen in the duodenal bulb in the film taken a few minutes after fluoroscopy. No duodenal ulceration was seen. Delay in stomach emptying time was marked and a 24 hr. film showed considerable barium retained within the stomach and only small amounts in the small and large intestine.

A diagnosis of congenital hypertrophic pyloric stenosis was made and a Fredet-Rammstedt operation was performed under open-drop ether anesthesia on the 3rd hospital day. Careful examination revealed no perforation in the duodenal mucosa. The patient had a normal postoperative course. Weight gain was satisfactory and on discharge after 18 hospital days he weighted 3,742 gm.

The infant continued to do well at home for the first few days. A few days before his second admission the number of stools increased to 5 to 6 daily, moderately loose but not foul smelling or green in color. The evening of the 6th day after discharge he began to vomit everything taken by mouth, anorexia developed, and he was readmitted to the hospital 2 days later at the age of 9 wk.

Physical Examination: On admission the clinical appearance seemed out of proportion to the history. The most prominent feature appeared to be undernourishment and moderate dehydration. There was marked loss of subcutaneous tissue and fat. There was no definite clinical evidence of acidosis. His color was poor but there was no cyanosis. His temperature was 37° C. and he weighed 3,232 gm.

He was lethargic but responded to external stimuli. There was no skin rash or eruption. The anterior fontanel was depressed. The heart and lungs were normal. The abdomen showed a well healed 6 cm. scar in the right upper quadrant. The liver edge was palpable about 1 cm. below the coastal margin. The abdomen was soft and flat. The remainder of the examination was not remarkable.

From the Pediatric Service, Fitzsimons General Hospital, Denver.
(Received for publication June 15, 1949.)

Laboratory Data: On admission the RBC was 3.37 million/cmm.; WBC 28 thousand/cmm. with 53% neutrophils, 35% lymphocytes, 12% monocytes; hemoglobin 10 gm. (64%). The CO_2 volume per cent was 30.

Roentgenograms: RG of the abdomen 3 days after readmission revealed a moderate amount of gas within the large bowel and a small amount in the small bowel which could not be interpreted as abnormal at this age.

Course in Hospital: Initial therapy consisted of withholding fluids by mouth and the administration of intravenous fluids with adequate M/6 sodium lactate to correct the acidosis present. Penicillin, 50,000 units twice daily, was given intramuscularly and a 60 cc. blood transfusion given on the second day. His temperature remained normal and he showed definite improvement. He had 4 somewhat loose stools on the first day and 2 normal appearing stools on the second.

He was started on oral feedings of an electrolyte solution (Darrow's solution with 5% glucose) on the third day. He took this very well. On the afternoon of that day he passed a stool composed of partially digested blood. Red blood count at this time was 3.33 million/cmm.; WBC 9.1 thousand/cmm.; hemoglobin 12 gm. (73%). Blood platelets were 127,000; prothrombin time normal; bleeding time 50 sec.; clotting time (capillary tube method) 3 min., 45 sec. A transfusion of 60 cc. of whole blood was given. The infant looked well at this time.

From this time on, the infant never passed a normal stool. He had 7 more small bloody stools during the next 24 hr. The blood consisted essentially of changed blood clots. It was never bright red in color, nor did it appear tarry. The bowel movements were unaccompanied by evidence of pain or distress. Vitamin K in 2 mg. doses was given daily. Oral electrolyte solution was discontinued and he was thereafter maintained on intravenous fluids. The origin of the gastrointestinal bleeding was not known at this time.

About 36 hr. after the first bloody stool, he had an initial hematemesis consisting of a few cc. of dark, changed blood. This was followed by an episode of acute gastric dilatation with marked ballooning of the abdomen. A large amount (c. 30 cc.) of changed blood was removed by catheter from the stomach. He went into collapse but responded to a rapidly administered blood transfusion.

The surgeons felt that the patient was too poor a risk for surgical exploration at that time. The tentative diagnosis was an ulcerative lesion high in the intestinal tract below the level of the stomach.

Blood counts were done at frequent intervals (2 to 4 times daily) and blood transfusions given as indicated. The infant went into severe collapse again and became cyanotic on the 4th day. He was placed in an oxygen tent and responded to a blood transfusion given over a period of several minutes. Twitching in the extremities appeared and was controlled by 0.5 gm. calcium gluconate daily. He was started on streptomycin 0.05 gm. every 6 hr. and penicillin 100,000 u. 3 times a day.

Through that day and the next the infant showed periods of improvement followed by collapse. Blood transfusion was used on 4 occasions with good results. Continuous Wangensteen suction was used to prevent gastric dilatation. He continued to have 3 to 5 bowel movements daily consisting chiefly of blood clots. He looked somewhat improved on the 5th day and surgery was scheduled for the following morning.

One hour prior to surgery he again went into collapse. He became markedly cyanotic and his respirations dropped to 4 to 6 a minute. He responded only moderately to blood transfusion, coramine, adrenaline and caffeine sodium benzoate. His condition was so poor that surgery could not be considered. He passed another large stool of blood on the 7th hospital day, his respirations became jerky and irregular and he died 1 hr. later.

Autopsy: A complete postmortem examination was done 2 hr. after death. He was marasmic and dehydrated in appearance. He weighted 3,200 gm., measuring 57 cm. from crown to heel.

The brain revealed no gross or microscopic pathology. The lungs showed patchy atelectasis over the base of the lower lobes and some congestion. The thymus appeared small, weighing 3 gm., and was normal on microscopic examination. The heart, liver, pancreas, adrenals and kidneys were all normal. The mesenteric lymph nodes and spleen showed moderate congestion.

The gastrointestinal tract, from stomach to anus, contained a considerable amount of clotted blood. The peritoneal surfaces were all smooth and glistening. There was no evidence of volvulus, herniation or intussusception. There was no evidence of peritonitis.

The mucosa of the stomach was intact, somewhat thick, and contained two pinpoint mucosal

hemorrhages. There was no ulceration, no polyps and no gross areas of hemorrhage. The pylorus appeared thickened and firmly contracted. Over the anterior surface of the pylorus there was an irregular elevated, firm, grayish-black plaque parallel to the long axis of the pylorus, measuring 1.5 x 1.1 cm., which apparently covered the area of previous operation. This was adherent to the under surface of the liver.

A search was made for a duodenal ulcer which had been suspected clinically. None could be found in spite of careful inspection. However, after the stomach and duodenum had been in formalin for 24 hr., a prominent irregular, sharply demarcated ulcer was found on the posterior superior surface of the duodenum measuring 1.2 x 0.9 cm. and originating approximately 0.5 cm. from the pyloric sphincter. The edges were punched out and partly overhanging. The base consisted of necrotic tissue. The mucosa of the rest of the small and large intestine was intact, without evidence of ulceration, polyps, new growth formation or other source for hemorrhage. No Meckel's diverticulum was present.

Microscopic section through the operative site revealed the mucosa to be intact and the muscle layer to be prominent and possibly increased in thickness. Section into the ulcer margin showed the mucosa, submucosa and internal muscle layer to end abruptly. There was a mild diffuse infiltration of some lymphocytes, plasma cells and occasional leukocytes.

The base of the ulcer consisted of a thin, necrotic layer of loose areolar tissue containing relatively few inflammatory cells and applied to a thin layer of longitudinal muscle. In this area the subserosal tissue was moderately infiltrated by lymphocytes and plasma cells, and contained a few blood vessels showing no sclerotic changes. A blood vessel penetrated the muscularis, leading to the base of the ulcer, showing some thickening of its wall but still patent.

Comments on Case

1. One questions the relationship of the Fredet-Rammstedt operation to the subsequent development of the duodenal ulcer. The operation had been performed with no undue trauma and the duodenal mucosa had apparently not been injured.

2. Roentgenographic studies using barium four weeks prior to the onset of bleeding did not reveal an ulcer.

3. It is difficult to explain how this ulcer escaped careful initial inspection at autopsy, since several persons had watched the inspection closely and with great interest. The finding of the ulcer after formalin fixation was analagous to the developing of a picture. Kennedy reported on this phenomenon in 1924.[1-3]

4. Forceful support and early surgery might have saved the infant.

Incidence

Peptic ulcer in infants in a relatively rare condition. It is probably not as rare as is generally thought. More than 300 cases have been recorded in the world literature[5-6] and undoubtedly many more have been observed but not reported. The first recorded case of gastric ulcer is that of Siebold[7] in 1825. He reported perforation of a gastric ulcer in an infant 2 days old. The first case of duodenal ulcer was reported by Hecker and Buhl[8] in 1864. By 1922 Paterson[4] was able to find 100 cases of duodenal ulcer in infants in the literature.

The rarity of the disease is borne out by the following studies: Holt[9] in 1913 found that in 1,800 postmortem examinations, 90% on children under 1 year of age, peptic ulcer was found only four times. Schmidt[10] in Germany, in 1913, reported peptic ulcer in 20 cases of 1,109 autopsies on children under 1 year of age. Bonnaire, Durante and Escalle[11] in France reported on 4,000 autopsies of newborn infants in 1914 in which only two cases of duodenal ulcer were found. Other series are much the same.[12-14]

Age and Sex: The sex incidence is interesting in that, unlike the striking preponderance

of men among adult patients, the distribution of the disease is equal between the sexes in infancy and childhood. This has led one group of authors[15] to postulate the theory that as puberty approaches and estrogens are elaborated by the female, these substances exert a specific effect in protecting the mature woman from peptic ulcer.[16] Estrogens have been administered to adult patients for therapeutic purposes but results have not been particularly striking.[17,18]

Peptic ulcer has been reported in every age group. Lee and Wells[19] reported a case of perforated gastric ulcer occurring in utero. Their infant had projectile vomiting at birth which continued during the first two weeks of life. RG showed an hour-glass contraction of the stomach, and on operation there were old organized adhesions around the ulcer area which were felt to represent a mechanism starting some time in utero.

Helmholz[20] in 1909 reported nine cases of duodenal ulcer in infants under 4 months of age. In 1913, Holt[9] collected and studied 95 cases of duodenal ulcer in infants under 1 year of age. Of those reported, 70% were between the ages of 6 weeks and 5 months, about 10% occurring in the newborn period. The greatest frequency was observed between the sixth and tenth week. Only seven patients were over 5 months of age.

Bird, Limper and Mayer[5] list the following figures in their group of 245 cases from the literature, 119 of whom were operated on and most of the others confirmed at autopsy:

Newborn (0-14 days)	42
15 days to 1 yr.	54
2-6 yr.	20
7-11 yr.	57
12-15 yr.	72
	245

There are some patients whose clinical course is suggestive of peptic ulcer but in whom signs and symptoms clear and they recover without confirmation by RG or operation. Lincoln, Nuzum and Browning[21] have reported cases in which infants bled from the bowel in the first week of life. Various signs indicated that peptic ulceration was present and the infants survived.

Proctor[22] reviewed 1,000 cases of duodenal ulcer in adults at the Mayo Clinic. He found that 26 patients in the group had the onset of their disease with symptoms in early childhood. Likewise, in 1,000 cases of gastric ulcer, 16 of the patients had symptoms dating back to childhood, even to the age of 4 to 5 years.

Etiology

The etiology of duodenal ulcer in infancy is unknown. The condition has been attributed by different authors to various causes. It may be due to a combination of factors.

The role that psychosomatic factors may play in the disease in infancy is undetermined and hard to evaluate in newborn infants.

External trauma, vascular, bacterial, chemical and neurogenic theories have been invoked to explain the etiology.

External Trauma: This has been the subject of many reports in the European literature. In this country Crohn and Gerendasy,[23] and Gray[24] have written reviews on the relationship between external trauma and peptic ulcer. Acute peptic ulcer following trauma to the abdomen and confirmed by autopsy has been reported.[25,26] Experimentally produced

ulcer in animals tends to heal readily.[24,27] The onset of peptic ulcer symptoms occurring soon after trauma does not establish trauma as the immediate cause even in the absence of a previous history of ulcer.[28] There is no experimental proof that external injury is capable of producing chronic ulcer.[28–30]

Vascular Theory: Virchow felt that only a local cause, such as thrombosis, embolism, spasm and endarteritis involving the small nutrient vessels, could account for a localized lesion such as a round peptic ulcer.[31,32] Others believe that the vascular changes which are found in association with peptic ulcers are probably secondary to the ulcer and not the cause of it.[33,34]

Wilkie[35] asserted that the pyloric end of the stomach and the first part of the duodenum have a relatively poor arterial blood supply. Reeves[36] stated that the arterial plexus of the submucosal coat of the lesser curvature of the stomach and duodenal cap is made up of fewer and smaller vessels than the remaining parts of the stomach and duodenum. Many of these vessels are end arteries with few anastomoses.[37] However most anatomic studies have shown that the entire stomach and duodenum are well supplied with numerous arterial branches capable of forming anastomotic channels. Therefore local infarction due to a decreased blood supply in the end arteries would tend to be a very uncommon occurrence.[28,38] Alvarez[39] stated that if arterial degeneration were a common cause of ulcer one would expect to find the disease beginning commonly in elderly people and not, as is the case, in a much younger age group.

Infection: Peptic ulcer has been produced experimentally by intravenous injection of pyocyaneous bacillus, dysentery bacillus, lactic-acid bacillus and the colon bacillus into dogs, guinea pigs and rabbits.[40] Rosenow[40] stressed foci of infection as an important etiologic factor. He was able to produce acute ulcers in the stomach and duodenum in 60 of 117 animals by injecting strains of streptococci recovered from resected human peptic ulcer and from foci of infection in the nose and throat of ulcer patients.

Gerdine and Helmholtz[41] felt that peptic ulcer could occur in epidemic form. They found Streptococcus viridans in 18 of 22 cases in infants and children.

Dunham and Shelton[42] reported a case of multiple gastric ulcers in a newborn infant with staphylococcus septicemia. Mills[21] reported a case of gastric ulcer hemorrhage in an infant 6 days old. The infant had gastrointestinal symptoms on the fourth day and blood appeared in the vomitus and stools on the last day. Autopsy revealed multiple gastric ulcers and streptococci were found in the inflammatory tissue about the ulcers and in the sloughing debris.

Emery and Monroe[43] found a recurrence of ulcer symptoms in 167 of 1,279 adult patients with peptic ulcer following attacks of respiratory infection. However, they found no greater incidence of foci of infection among several hundred peptic ulcer patients than in a control series of patients without ulcer.

Chemical Factors: Peptic ulcer does not occur in the complete absence of gastric juice.[28,44] It occurs only in those portions of the gastrointestinal tract exposed to the acid of gastric secretion. Washburn and Rozendaal[45] and Kahn[46] reviewed 1746 consecutive cases of pernicious anemia, which is associated with achlorhydria, without finding a single instance of peptic ulcer.

Miller[47] studied gastric acidity during the first month of life. He found that the heavier an infant is at birth the more likely is it to have a more perfectly developed gastric mucous membrane and potent gastric secretion. A maximum acidity in the fasting juice is reached during the first day of life. It then falls during the next 10 days and thereafter gradually

rises, usually not reaching the earlier level until the age of 3 years.[48,49] Achlorhydria is common in premature infants. Also it was observed in 10 out of 13 infants suffering from cerebral hemorrhage.

Burns: In 1842 Curling reported 10 cases of duodenal ulcer associated with burns. The immediate cause of death was perforation with peritonitis in three of his cases and hemorrhage in six. Such ulcers are commonest in children, the average age in Curling's series being 10.8 years. It has an estimated incidence in fatal cases of 6%.[50]

The ulceration is acute in character and it may occur as an early or late complication. The lesion usually develops during the third or fourth week of illness, when the patient has apparently recovered from the critical stage of the burn. The symptoms and clinical course are the same as in ordinary peptic ulcer. The condition is prone to be overlooked in view of the severe constitutional and systemic manifestations which follow burns.[50]

Neurogenic Theory: According to Vonderahe,[51] Rokitansky made the following statement more than one hundred years ago: "Perhaps the proximate cause may be looked for in diseased innervation of the stomach, owing to a morbid condition of the vagus, and to extreme acidification of the gastric juice."

Cushing[52] stated that after major intracranial operations the vomitus may show evidences of changed blood for the first few days. He observed three cases of acute perforation of the upper gastrointestinal tract occurring shortly after operations for intracranial tumors. Beattie[53,54] noted increase in peristalsis and secretion in the stomach, together with patches of hyperemia of the mucous membranes, on stimulating the floor of the third ventricle; these effects were abolished after section of the vagus nerve.

Cushing[52] wrote: "The parasympathetic apparatus, in all probability, under normal conditions is likewise strongly affected by cortical or psychic (Pavlov) influences. However this may be, direct stimulations of the tuber (cinereum) or its descending fiber tracts, or what theoretically amounts to the same thing, a functional release of the vagus from paralysis of the antagonistic sympathetic fibers, lead to hypersecretion, hyperchlorhydria, hypermotility and hypertonicity, especially marked in the pyloric segment. By the spasmodic contractions of the musculature, possibly supplemented by accompanying local spasms of the terminal blood vessels, small areas of ischemia or hemorrhagic infarction are produced, leaving the overlying mucosa exposed to the digestive effects of its own hyperacid juices."[52]

Opper and Zimmerman[55] observed the occurrence of ulcerations in the esophagus, stomach and duodenum in 21 patients who had varying lesions in the midbrain, interbrain and cerebral cortex. Mossberger[56] reported on a case of a solitary punched out peptic ulcer in a newborn infant associated with a small midline growth of the tuber cinereum. The infant was 5 days old and had a perforated duodenal ulcer. Vonderahe[51] reviewed 51 cases of gastroduodenal ulceration and noted well marked localized pathologic alterations of the brain or its membranes in 21.6% of them.

The mechanism of the cerebral circulation and the evidence for the hypothesis that vasomotor factors are related to local variability in cerebral circulation thereby affecting parasympathetic and other centers is presented by Cobb,[57] Bailey[58] and Wolff.[59]

Pathology

Duodenal ulcers may be easily overlooked at necropsy because they may be very small and obscured by blood, mucus or fibrin. They are usually on the posterior wall, nearer the papilla than the pylorus. Gastric ulcers are generally situated on or near the lesser curva-

ture. Duodenal ulcers outnumber gastric ulcers in a ratio of two to one.[5] Perforation is more frequent in gastric ulcers.[60]

In infancy the ulcers are more commonly of the acute type. There is minimal induration or round cell infiltration, with evidence of destruction and none of repair.[5] They may be associated with necrosis and hemorrhage including surrounding tissues rather than with inflammation.

The ulcers vary in size from 2.3 mm. to 1.5 cm. They may be oval or circular, single or multiple. Multiple ulcerations occur either in the stomach or duodenum. As many as five separate and distinct ulcers have been found in the same infant.[5]

The great majority, at least of those that are recognized, bleed seriously or perforate or do both. In the newborn period, peritonitis following perforation is often delayed since the duodenal contents are relatively sterile. The only clue clinically may be acute collapse. Hemorrhage may be concealed, the intestinal tract revealing large clots, with no apparent bleeding during life.[5]

Diagnosis

Peptic ulcer in infancy is atypical and for this reason the diagnosis is overlooked in many instances. The condition is practically never diagnosed or suspected until hemorrhage or perforation occurs. The general impression gained from the literature is that duodenal ulcer in infants is, unfortunately, largely a postmortem diagnosis.

In a little more than one third of the recorded cases, no symptoms which could be attributed to ulcer were present during life, the condition being found at autopsy in infants dying of intercurrent disease or of marasmus.

Bleeding: Hemorrhage is the only definite sign pointing to duodenal ulcer. Melena is present in approximately one half of the cases[9] and may be in small or large amounts. Once gross hemorrhage has occurred, it is apt to persist until death of the patient, which usually comes within 2 to 36 hours after its first appearance. The loss of a small amount of blood may produce a serious state. In several cases the collapse has been so acute and so severe as to suggest perforation, though the autopsy revealed intestinal hemorrhage.[5]

Hematemesis is less frequent than melena and may occur either alone or with the latter. It is either bright red or coffee-grounds in appearance. It is usually small in amount, although as much as one half to one ounce has been recorded in the newborn infant.[5]

Perforation: Whenever there is sudden collapse in an infant, the possibility of perforation of an ulcer must be considered. After the development of the first symptoms of collapse due to perforation, death usually ensues within 24 hours. Collapse may appear with no antecedent signs.

Vomiting: Duodenal ulcer may be associated with spasm of the pylorus[61] and less commonly with pyloric stenosis.[62,63] There may be vomiting, loose stools with some dehydration and acidosis, to be followed suddenly without warning by bloody vomitus or melena. A previously scaphoid abdomen may become distended due to perforation of the ulcer. When symptoms suggesting pyloric stenosis are seen for the first time in an infant over 3 to 4 months of age, duodenal ulcer should be borne in mind as a possible explanation.

Roentgenogram: Roentgenographic studies as an aid in diagnosis were first reported by Pedrazzi[64] in 1927. Stern, Perkins and Nessa[65] in 1929 reported a case of a 2 day old

infant in whom barium was instilled into the stomach by means of a catheter and a niche was revealed on the lesser curvature near the pylorus. Roentgenographic studies may occasionally reveal the lesion, but it is not as easily demonstrable as in adults. Because of the danger of aspiration in these patients, lipiodol is felt to be a safer contrast agent than barium.

Treatment

Early diagnosis is important inasmuch as the majority of cases with prominent symptoms are surgical and a fatal outcome may be the result of delay. Infants stand the loss of blood poorly, and in face of continued hemorrhage expectant medical treatment is unwise. In view of the reports of fatalities from bleeding, transfusion should be resorted to early and must be given in adequate amounts to sustain the infant until surgery can be performed.

In the very young the indications for operation include: perforation, hemorrhage, pyloric stenosis and persistent pylorospasm.

Bird, Limper and Mayer[5] in 1941, made a study of 119 cases treated surgically in the first 2 years of life. The mortality was 70%. The youngest survival was a 34½ hour old baby with perforation of a duodenal ulcer. The next in age to survive was reported by Selinger[66] in a male aged 3 months with perforation of the stomach. No cases of serious bleeding with subsequent recovery were found in the literature reviewed.

Summary

A fatal case of hemorrhage in an infant 10 weeks of age due to a bleeding duodenal ulcer is presented.

The relative infrequency of duodenal ulcer in infancy is cited. The relationship to trauma and burns and to vascular, chemical and neurogenic theories are discussed. Diagnosis, including the use of roentgenograms, is presented. Hemorrhage is the only definite sign pointing to duodenal ulcer. After persistent vomiting, with or without blood, plus melena and the appearance of sudden collapse, the possibility of peptic ulcer should be considered.

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NEWS AND ANNOUNCEMENTS

CEREBRAL PALSY INSTITUTE

A 2 week Institute in Cerebral Palsy, for qualified physicians, nurses, physical, occupational and speech therapists, social service and guidance workers, and teachers, has been announced by Dr. Philip D. Wilson, President of The Coordinating Council for Cerebral Palsy in New York City, Inc., 270 Park Avenue, New York City. The Institute will be held for a 2 week period beginning Monday, November 6, and will include lectures, clinical demonstrations and seminars.

Following the Institute, opportunities for a 3 month in-service training course will be available to a limited number of physicians and therapists.

Further information can be obtained from Miss Marguerite Abbott, Executive Director of the Council, 270 Park Avenue, New York 17.

* * *

The following appointments as heads of departments of pediatrics have been announced: Leonard Tomb Davidson, M.D., University of Louisville, Louisville; Merl John Carson, M.D., University of Southern California, Los Angeles; John A. Adams, M.D., University of California at Los Angeles.

* * *

A continuation course in Child Psychiatry for pediatricians and physicians will be presented at the Center for Continuation Study November 27 to December 1. Dr. Ralph D. Rabinovitch and Dr. John Waterman will participate as lecturers and group discussion leaders. Dr. Reynold A. Jensen, Head of the Child Psychiatry Service of the University of Minnesota, is in charge of the arrangements for the course and will also act as lecturer and group discussion leader.